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Millennium X16062

Ixazomib, Oral Metronomic Cyclophosphamide and Dexamethasone for First-Line Treatment of Multiple Myeloma: A Phase II Brown University Oncology Group Study.

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1.0 OBJECTIVES

1.1 PRIMARY OBJECTIVE:

1.1.1 To evaluate the response rate of Ixazomib with metronomic cyclophosphamide and dexamethasone for first-line treatment of multiple myeloma

1.2 SECONDARY OBJECTIVES:

1.2.1To evaluate the toxicities associated with Ixazomib with metronomic cyclophosphamide and dexamethasone.

1.2.2 Estimate the progression-free survival and overall survival of Ixazomib with metronomic cyclophosphamide and dexamethasone for first-line treatment of multiple myeloma

2.0 BACKGROUND

Bortezomib, cyclophosphamide and dexamethasone (CyBorD) for myeloma: There will be an estimated 22,000 individuals diagnosed with multiple myeloma in the United States in 2013 and 11,000 deaths (1). Newly diagnosed myeloma patients are treated with induction therapy. Many patients if eligible, proceed to an autologous stem cell transplant. The goal of initial therapy is to induce the deepest remission possible.

CyBorD (Cyclophosphamide, bortezomib, dexamethasone) is a commonly utilized first-line treatment for myeloma. CyBorD demonstrates improved near complete and very good partial responses (41%, and 67%, respectively), as compared to lenalidomide and dexamethasone (35% and 47%, respectively) and cyclophosphamide, lenalidomide, and dexamethasone (15% and 47%, respectively) (2). ***The goal of this proposal is to improve on this activity by substituting bortezomib with a next generation proteasome inhibitor and utilizing metronomic cyclophosphamide.***

Next Generation Proteosome Inhibitors: Next generation proteasome inhibitors have increased efficacy and less toxicity than bortezomib (3). Ixazomib (MLN 9708) is a potent reversible 20s proteasome inhibitor. Exposure to an aqueous solution rapidly hydrolyzes Ixazomib to its biologically active form, MLN 2238 (4). Anti-tumor activity in murine and cell line multiple myeloma models has been demonstrated (4, 5). In preclinical studies, MLN 2238 shows greater anti-tumor efficacy than bortezomib. The added efficacy is thought to be secondary to its faster dissociation in blood, which prevents red blood cells, and their high proteasome content, from sequestering much of the drug. More bioactive drug available in turn leads to Ixazomib's greater tissue penetration than bortezomib (6).

The initial phase I studies of Ixazomib, in heavily pretreated relapsed/refractory patients, administered Ixazomib twice weekly. The most common toxicities were fatigue and thrombocytopenia. Only 8% of patients experienced peripheral neuropathy and none higher than grade 2. Six of 36 (17%) heavily pretreated patients responded including patients refractory to bortezomib. The maximum tolerated dose was 2.0mg/m^2. In pharmacokinetic studies, the half-life of Ixazomib was determined to be 4-5 days (7). More recently Ixazomib was administered weekly in combination with lenalidomide and dexamethasone. The overall response rate was 88% including 18% with a complete response and 40% with a very good partial response. ***These data suggest that Ixazomib is at least as effective as bortezomib with less neurotoxicity.***

Metronomic Cyclophosphamide: CyBorD utilizes bolus cyclophosphamide on days 1, 8 and 15. Metronomic dosing (continuous daily administration) gives a continuous dose of drug to target cells as they move through the cell cycle thereby creating sustained apoptotic activity in addition to modulation of the immune tolerant microenvironment via eradication of immunosuppressive lymphocytes (8, 9). ***This has been hypothesized to be highly efficacious in myeloma since continuous dosing may impact the tumor milieu, particularly angiogenesis.***

Initial clinical trials of metronomic cyclophosphamide suggest this may have superior efficacy. For example, a phase II study of metronomic cyclophosphamide and prednisone demonstrated a 67% response rate (10). A second study of metronomic cyclophosphamide (50mg/day) combined with dexamethasone and bortezomib demonstrated a response rate of 90% (11) and a trial of continuous cyclophosphamide, thalidomide and prednisone demonstrated a response rate of 63% (12).

RATIONALE AND SUMMARY OF CURRENT PROPOSAL:

CyBorD is one the most commonly utilized front-line regimens in multiple myeloma. The goal of this proposal is to develop a more effective and better tolerated regimen. Ixazomib appears to have greater activity than bortezomib with less peripheral neuropathy. Metronomic cyclophosphamide may be a more active administration schedule than bolus cyclophosphamide in myeloma in part since it may target the tumor microenvironment especially effecting angiogenesis. Herein, we propose a Phase II study of Ixazomib with metronomic cyclophosphamide and dexamethasone.

During the first month of treatment, patients will receive Ixazomib once weekly on days 1, 8, and 15 with dexamethasone and continuous cyclophosphamide 50 mg/day. Patients will then receive Ixazomib twice weekly (on days 1, 4, 8, 11, 15 and 18) during cycles 2-6 with twice weekly dexamethasone and continuous cyclophosphamide provided treatment is tolerated during cycle 1. For patient safety, a less intensive schedule is utilized in the first month of treatment since patients may have extensive bone marrow involvement with myeloma at study onset – "debulking" of marrow tumor in the first cycle may improve tolerance in subsequent cycles of therapy facilitating twice weekly Ixazomib beginning in the second cycle of treatment. Each patient will be dose escalated in this manner. The rationale is to deliver a patient specific maximal level of drug for a potential improved therapeutic efficacy. The Brown University Oncology Research Group and PI will perform an early safety assessment after the first 6 patients have completed 2 cycles of treatment. A total of 20 patients will be evaluated for efficacy.

3.0 PATIENT ELIGIBILITY

3.1 Conditions for Patient Eligibility

3.1.1 Age ≥ 18 years of age

3.1.2 Histologically confirmed multiple myeloma according to WHO classification. Pathology report to be sent to BrUOG for confirmation

3.1.3 Diagnosis of Multiple Myeloma that has not been previously treated (although patients that received emergent steroid and/or local radiation therapy will be permitted to enter the study). Patients can still be on steroids at time of registration and treatment start, but should be on a tapering dose. Details need to be submitted to BrUOG with dates and doses.

3.1.4 Measureable disease defined as either an elevated serum M-protein, urine M-protein, bone marrow involvement ≥30% or serum free light chains per the IMWG criteria. Confirmation to be sent to BrUOG, see section 7 for criteria

3.1.5 Life expectancy of ≥ 6 months, confirmation per treating investigator required

3.1.6 Absolute neutrophil count (ANC) ≥ 1,000/mm^3 and platelet count ≥ 75,000/mm^3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment. If transfusional support provided, please document for submission to BrUOG

3.1.7. Calculated creatinine clearance ≥ 30 mL/min (based on the Cockcroft-Gault Equation below) also see section 11.2:

For males:

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

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})}$$

3.1.8 ECOG performance status of 0-1.

3.1.9 Adequate Liver function; AST or ALT < 3.0 x upper limit of normal (ULN); Total bilirubin <1.5x ULN

3.1. 10 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.

3.1.11 Female patients who:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR
- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug and obtain a pregnancy test, which must come back negative prior to drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject and obtain a serum pregnancy test, which must come back negative prior to drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Documentation and confirmation of conversations and patient commitment to contraception is required to be noted and sent to BrUOG. Female's menopausal status to be documented and submitted to BrUOG if applicable. Pregnancy test, if applicable, required to be sent to BrUOG.

3.1.12 Male patients, **even if surgically sterilized** (ie, status post-vasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through *90 days* after the last dose of study drug, OR

- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Documentation and confirmation of conversations and patient commitment to contraception is required to be noted and sent to BrUOG.

3.2 Conditions for Patient Ineligibility

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

3.2.1Female patients who are lactating or have a positive serum pregnancy test during the screening period.

3.2.2 Any surgery within 14 days before enrollment.

3.2.3 Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.

3.2.4 Central nervous system involvement (myeloma-related).

3.2.5 Active infection requiring systemic antibiotic therapy or other serious active infection within 7 days before study enrollment (7 day wash-out period post end of antibiotics)

3.2.6 Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

3.2.7 Systemic treatment, within 14 days before the first dose of ixazomib, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

3.2.8 Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

3.2.9 Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol. If not applicable, then investigator to document not applicable

3.2.10 Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. If not applicable, then investigator to document not applicable

3.2.11 Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing. If not applicable, then investigator to document not applicable

3.2.12 Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection. No amyloid deposition.

3.2.13 Patient has ≥ Grade 2 peripheral neuropathy or Grade 1 with pain.

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

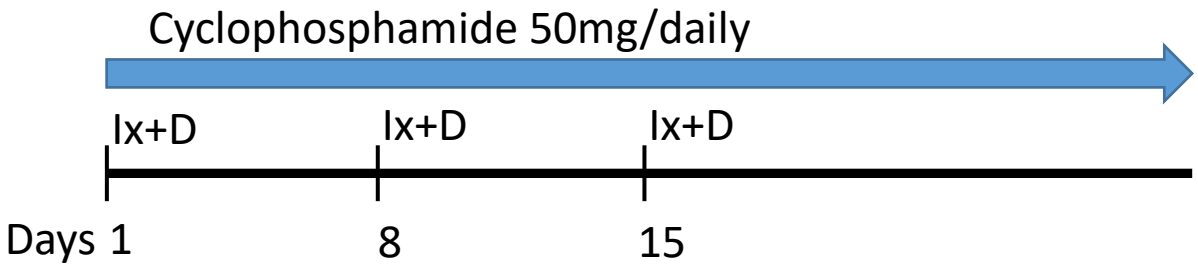
3.3 Re-screen:

If a patient signs consent and then screen fails (does not meet the eligibility criteria) and the treating MD requests that the patient be re-screened outside of the 28 day screening window, sites are to contact BrUOG who will assess patients on a case by case basis. Depending on many diverse factors including the conditions that are being evaluated, the reasons why patient initially screen failed, and the nature of the initial results, re-screening may or may not be medically/scientifically appropriate. BrUOG should be made aware of such a situation with at least 72 hours and provided with information on screen-failure.

4.0 TREATMENT

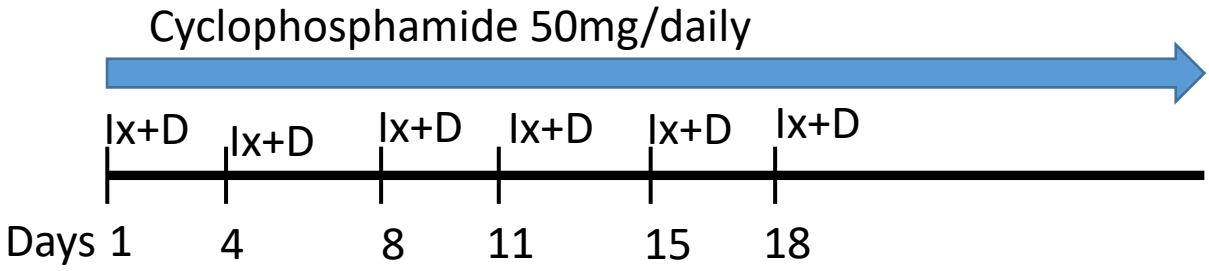
Induction Phase: During the induction phase all patients will begin by receiving cycle # 1 as described below with dosing of Ixazomib and Dexamethasone on days 1,8,15. Patients will then be assessed based on toxicities outlined below, to determine if during cycles 2-6 they can be moved to twice weekly dosing or if they must remain on once weekly dosing. Post cycle 6, see "Maintenance Phase" language below for guidance.

Cycle #1: (1 cycle = 28 days)



- Cyclophosphamide: 50 mg/day continuous daily
- Ixazomib: 4mg/day 1, 8, 15
- Dexamethasone: 20 mg/day 1, 8, 15
- A +/- 2 day window is provided for dosing to accommodate holidays or scheduling. Dosing days cannot be within a 24 hour window of each other.

Cycles 2-6



- Cyclophosphamide: 50 mg/day continuous daily
- Ixazomib: 4mg/day 1, 4, 8, 11, 15, 18
- Dexamethasone: 20 mg/day 1, 4, 8, 11, 15, 18

- A +/- 2 day window is provided for dosing to accommodate holidays or scheduling. Dosing days cannot be within a 24 hour window of each other.

To proceed from the schedule of once-a-week Ixazomib and dexamethasone (weeks 1, 2 and 3) in cycle #1 to twice-a-week Ixazomib and dexamethasone (weeks 1, 2 and 3) in cycles 2-6, patients must not experience, in cycle #1 any of the following:

- Grade 3 or Grade 4 Neutropenia
- Grade 3 or Grade 4 thrombocytopenia
- Febrile neutropenia
- Treatment related Grade 3 or 4 Non-Hematology toxicity
- Treatment related Grade ≥ 2 Neuropathy

Patients who experience the above toxicities will have dose reductions as mentioned in section 5.1 and will not be dose escalated to the twice weekly dosing.

A patient's cycle may be delayed up to 4 weeks (post cycle 4) to accommodate collection for autologous stem cell transplant. Documentation is required to be submitted to BrUOG for this.

Treatment (post cycle 6 onward): Maintenance Phase:

- After the completion of Cycle #6, patients have the option of proceeding to autologous stem cell transplantation. If the patient goes to autologous transplant, they will then come off study and be followed per schedule evaluation
- If they do not go to autologous transplant, they will receive maintenance ixazomib at 4 mg days 1, 8 and 15 of a 28 day cycle for 1 ½ years (to complete 2 years of protocol treatment) or until relapse.
- A +/- 2 day window is provided for dosing to accommodate holidays or scheduling

4.1 Administration:

4. 1.1 Ixazomib: All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of ixazomib should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of ixazomib dose (see section 5.0).

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Millennium as capsules of or as capsules of 2.3-, 3.0- and 4.0 mg ixazomib.

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

For once weekly dosing: Missed doses can be taken as soon as the patient remembers (within 48hrs/2 days of the missed dose) if the next scheduled dose is 72 hours or more away. For twice weekly dosing: Missed doses can be taken as soon as the patient remembers (within 24hrs/1 day of the missed dose) if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

4.1.2: Cyclophosphomide should be taken in the morning preferably with food to reduce stomach upset. The use of proton pump inhibitors or H2 blockers will be up to the discretion of the treating physician

4.1.3 Dexamethasone should be taken in the morning preferably with food to reduce stomach upset. The use of proton pump inhibitors or H2 blockers will be up to the discretion of the treating physician

4.2 Precautions and Restrictions

- Fluid deficit should be corrected before initiation of treatment and during treatment.
- Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

4.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study.

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted in this study. (A drug-drug interaction [DDI] with a strong inhibitor would increase the ixazomib exposure and could lead to a higher probability of an AE.):

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use (Rationale: 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 within 3 days prior to study drug dosing are not allowed to help patients meet eligibility criteria or before any dosing day

4.4 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 (eg, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted, except for cycle 1, however therapeutic use in response to a confirmed grade 3 or 4 neutropenia during cycle 1 will be allowed. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the Millennium Clinical or Medical Representative . Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- All patients must be placed on prophylactic doses of either acyclovir, valacyclovir, or famvir.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Supportive measures consistent with optimal patient care may be given throughout the study.

5.0 TOXICITIES, DOSE MODIFICATIONS, AND MANAGEMENT

5.1 Dose Levels For Ixazomib and Cyclophosphamide

Table 1

Dose Level	Ixazomib Dose (mg)	Cyclophospamide Dose (mg)	Dexamethasone Dose (mg)
Starting Dose	4.0 mg	50 mg/day	20
-1	3.0 mg	25 mg/day	See section 5.7
-2	2.3 mg	25 mg QOD	See section 5.7
-3	Discontinue	Discontinue	Discontinue

Patients requiring a dose delay of > 2 weeks due to treatment related toxicities will have a permanent 1 dose level reduction as per section 5.1. If the patient continues to fail to meet the above-cited criteria, there will be a delay of therapy and re-evaluation. Treatment must be discontinued if patient experiences treatment related toxicity with delay of> 3 weeks.

5.2 Criteria for moving from once weekly treatment to twice weekly treatment (during induction)- all patients: To proceed from the schedule of once-a-week Ixazomib and dexamethasone (weeks 1, 2 and 3) in cycle #1 to twice-a-week Ixazomib and dexamethasone (weeks 1, 2 and 3) in cycles 2-6, patients must ***not*** experience, in cycle #1:

- Grade 3 or Grade 4 Neutropenia
- Grade 3 or Grade 4 thrombocytopenia
- Febrile neutropenia
- Treatment related Grade 3 or 4 Non-Hematology toxicity
- Treatment related ≥ Grade 2 Neuropathy or Grade 1 neuropathy with pain

Patients who experience the above toxicities will have dose reductions as mentioned in section 5.1 and will not be dose escalated to the twice weekly dosing.

5.3 Criteria for Beginning or Delaying a Subsequent Treatment Cycle & Dose Modifications for Treatment Associated Toxicity during induction:

Treatment with ixazomib, cyclophosphamide and dexamethasone will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm3.
- Platelet count must be ≥ 75,000/mm3.
- All other treatment related non-hematologic toxicity (except for alopecia or weight gain/loss) must have resolved to ≤ Grade 1 or to the patient's baseline condition. (See table 4 as well)

If the above toxicity is noted, all three medications will be held until the above criteria are met. Patients requiring a dose delay of > 2 weeks due to treatment related toxicities will have a permanent 1 dose level reduction as per section 5.1. If the patient continues to fail to meet the above-cited criteria, there will be a delay of therapy and re-evaluation. Treatment must be discontinued if patient experiences treatment related toxicity with delay of> 3 weeks.

5.4 Criteria for Beginning or Delaying a Subsequent Treatment Cycle for Treatment Associated Toxicity during maintenance:

Treatment with ixazomib will use a cycle length of 28 days (days 1, 8, 15). For a new cycle of treatment (day 1) to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm3.
- Platelet count must be ≥ 75,000/mm3.
- All other treatment related non-hematologic toxicity (except for alopecia or weight gain/loss) must have resolved to ≤ Grade 1 (excluding alopecia) or to the patient's baseline condition. (See table 4 as well)

If the patient continues to fail to meet the above-cited criteria, there will be a delay of therapy and re-evaluation.
Treatment must be discontinued if patient experiences treatment related toxicity with delay of> 3 weeks.
Patients requiring a dose delay of > 2 weeks due to treatment related toxicities will have a permanent 1 dose level reduction- see table 5.1 . Patients who are dose reduced will not be re-escalated.

5.5 Dosage adjustments of Ixazomib and cyclophosphamide for hematologic toxicity during a cycle (both induction and maintenance).
For induction: Dose reductions of dexamethasone are not required for hematologic toxicity, for induction below table refers to days when Ixazomib and cyclophosphamide are taken or days when cyclophosphamide is taken alone and labs are taken. For induction, on days when Ixazomib and cyclophosphamide are taken together, patients are to be instructed to not take Ixazomib or cyclophosphamide until after the results from their labs are confirmed. For days when patients are taking cyclophosphamide alone, they do not need to hold their drug for results, but if results correlate to 5.5 hold requirements for PLT and ANC, then hold cyclophosphamide next day and repeat labs as noted below until values recover.
For maintenance: As Ixazomib is the only drug given during maintenance, the below table refers to Ixazomib dosing only and will correlate to labs taken prior to day 15 dosing.

Table 2

Criteria	Action
<u>Within-Cycle Dose Modifications</u> • If platelet count ≤ 30 × 10^9/L or ANC ≤ 0.50 × 10^9/L on a Ixazomib and/or cyclophosphamide dosing day (other than Day 1)	• Ixazomib and cyclophosphamide dose should be withheld (skip dosing day). Dexamethasone will still be given as per schedule. • Complete blood count (CBC) with differential should be repeated at least every other day until platelet count > 30 × 10^9/L or ANC > 0.50 × 10^9/L. Ixazomib and cyclophosphamide may then be reinitiated with 1 permanent dose level reduction.

5.6 Dosage adjustments of Ixazomib and cyclophosphamide for non- hematologic toxicity (induction as per toxicity assessment pre day 8 dosing).
Specific dose reductions for neuropathy are specified in Table 4. (Dose reductions of dexamethasone are not required for hematologic toxicity, non-hematologic toxicities related to dexamethasone are described in section 5.7)
Table 3

Criteria	Action
<u>Within-Cycle Dose Modifications</u> Grade 3 non-hematologic toxicity judged to be related to study drug (excluding alopecia)	• Hold Ixazomib and cyclophosphamide unti resolution to Grade ≤ 2 or baseline then resume at permanent dose level reduction (skip dosing day). (The investigator may choose to resume treatment when resolution to grade 2 or may wait until resolution to grade 1). For rash judged to be from Ixazomib dose reduce Ixazomib only. Dexamethasone is to be given even when Ixazomib and cyclophosphamide are not given. See section 5.7 for dexamethasone reductions.

Table 4	Ixazomib Treatment Modification For Neuropathy
Grade 1 with pain or Grade 2 or Grade 3 peripheral neuropathy	• Hold Ixazomib until resolution to Grade ≤ 1 and Reduce study drug to next lower dose
Grade 4 peripheral neuropathy	• Discontinue study drug

Table 4: For assessments prior to starting a new cycle, if patient experiences a neuropathy grade 1 with pain, grade 2 or grade 3, hold all drugs (then reduce as noted above) as instructed by sections 5.3 and 5.4. For mid-cycle assessments, if patient experiences a neuropathy grade 1 with pain, grade 2 or grade 3 study drug only would be held, see above table for instruction. For grade 4 peripheral neuropathy study drug will be stopped- see table 4.

5.7 Dexamethasone

In general, dose reduction of dexamethasone is not utilized. However, in the case of Grade 3 or 4 gastrointestinal bleeding, severe diabetes unresponsive to standard management or mental status changes dexamethasone must be held until adequate improvement, then dexamethasone dose may be reduced by up to 50% as per local institutional standards.

5.8 Management of Specific Toxicities

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.

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 will be initiated as clinically indicated. Other antivirals are also acceptable.

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.

Diarrhea

Prophylactic antidiarrheals should 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.

Erythematous Rash With or Without Pruritus

Rash with or without pruritus has been reported with Ixazomib. 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.

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. Please see section 5.5 on drug reduction.

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.

Neutropenia

Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice

Fluid Deficit

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

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

Hypotension

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

Posterior Reversible Encephalopathy Syndrome

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

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. If transverse myelitis occurs, the patient should be permanently removed from study therapy.

6.0 SCHEDULE OF EVALUATIONS / STUDY CALENDAR *The day an assessment (PE, labs, scan etc) is completed is day 0 for counting for example labs drawn on Friday can be used for Monday dosing as this is within 3 days*

Test	Pre-Study Screening ≤ 28 days prior to Registration: all required to be submitted (with results) to BrUOG prior to registration	Cycle 1F (within 3 days prior to day 1)	Cycle 2-6 (within 3 days prior to day 1)	Maintenance 28 days= cycle	End of Treatment (whether this be at any point coming off study, once completed 6 cycles or post coming off maintenance) within 2 weeks	30 days post last dose of drug	F/Ue
History	X						
Physical	X	Xfa	Xa	Q56 days (within 2 weeks) *to correlate and be done prior to a cycle beginning	X	X (plus one week)	
Vitalsb	X	Xfa	X ba	X b (within 72 hours prior to day 1 of cycle)	X b		X b
ECOG PS	X	Xfa	Xa	Q56 days (within 2 weeks) *to correlate to be done prior to a cycle beginning	X		X
CBC with differential and PLT	X	Twice weeklyf I (48 hours apart), required to be done prior to dosing (within 24 hrs + 1 day)	Twice weekly I (48 hours apart) see subscript I	Q2weeks(within 72 hours prior to day 1 and day 15 of a cycle)	X		Xe
Labsc	Xc	Xcfga	Xcga Prior to day 1 of drug	Xc Q28 days (within 1 week) *to be done prior to a new cycle beginning (day 1)	Xc		Xce
Myeloma Labsd	Xd	Xdfga	Xdga prior to day 1 drug	Xd Q56 days (within 2 weeks) * to be done prior to a cycle beginning (day 1)	Xd		Xde
ECG	X						
Toxicity AssessmentH	X	Xf a required prior to day 1 (see subscript f) and prior to day 8 dosing	X prior to day 1 and day 8 drugsga	Q56 days (within 2 weeks) * to be done prior to a cycle beginning (day 1)		X (days plus 1 week)H	
Documented Bone Marrow	X (within 8 weeks of study entry)				XJ		

Biopsy with cytogenetics (cytogenetics are not required to be resulted for registration)							
Skeletal Survey	X (within 8 weeks of study entry)						

[a] Within 3 days of each cycle day 1 (an additional day is provided for holidays)

[b] height(only screening), weight, BP ,pulse, Resp, Temp

[c] BUN, creatinine, bilirubin, glucose, alkaline phosphatase, ALT, AST, electrolytes (Na, K, C1, CO_2), Ca, Mg, PO4, albumin, B-2 microglobulin, Serum HCG (HCG is required only for patients who are women with childbearing potential (see eligibility) and must be done at day 1 (prior to drug) of each cycle-urine) For baseline only, required to draw HIV and hepatitis panel (HBsAg, Anti-HBs, Hep B core and HCV RNA and HCV antibody. Patients who are confirmed to be HCV antibody non-reactive and with no history of Hep C infection, HCV RNA is not required to be drawn). No labs required in follow-up once patient has been documented to have progressed.

[d] SPEP, IFE, UPEP, UIFE, serum free light chains Kappa, Lambda and Kappa/Lambda ratio, IgG, IgA, IgM with positive labs from screening followed at subsequent time points. 24 hour urine collection required for urine M protein UPEP and UIFE. For baseline, if patient has already had myeloma labs resulted within 3 months (≤ 3 months) prior to registration, these labs with results can be submitted as a place holder for BrUOG 299 myeloma labs. Myeloma labs **must** still be collected as noted above and drawn within 28 days of registration, however to avoid delays in registration, given results take time, prior results can be submitted along with confirmation that BrUOG 299 myeloma labs were drawn and are pending (documentation required). For patients who **do not** have measurable disease based on bone marrow involvement, prior myeloma labs must meet measurable disease criteria to be allowed for use at registration or otherwise results of BrUOG 299 myeloma labs must be resulted and confirmed to allow for registration. For patients with a negative UPEP at baseline, UPEP and UIFE is not required post baseline, but if done must be submitted to BrUOG. No longer required in follow-up once patient has been documented to progress. Post baseline, if insurance does not cover myeloma labs and labs are thus not drawn, it will not be considered a deviation but sites must report this to BrUOG. If patient has myeloma labs drawn for a cycle and cycle is then delayed, they do not need to be re-drawn prior to dosing unless the delay is >2 weeks from when it was scheduled.

[e] Follow for survival and recurrence every 6 months (+ 2 weeks) for 5 years and document on follow up form; no labs required after patient has been documented to progress.

[f] labs can be used for cycle 1 day 1 if they are within 28 days of treatment, however CBC with differential and PLT, BUN and Creatinine can only be used if they are within 7 days of cycle 1 day 1, otherwise they must be drawn and resulted before dosing on day 1 cycle 1. Baseline myeloma labs can be used for cycle 1 day 1 if they are within 28 days of treatment. Physical, vitals, PS, toxicity assessment can be used for cycle 1 day 1 if they are within 28 days of treatment.

[g] To be drawn prior to cycle day 1 dosing within 3 days.

[H] pregnancies or suspected pregnancies are to be reported to BrUOG while patient is on drug and for up to 90 days post last dose of drug. See section 11.3.1. SAEs are to be reported from time patient's signs consent to 30 days post last dose of drug. **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.**

I: CBC with differential and PLT to be drawn twice weekly cycle 1 including the week off of dosing. CBC with differential and PLT to be drawn twice weekly cycle 2, prior to drug administration for dosing decisions within 24 hours (1 day) (an additional day provided for holidays or scheduling). If there is no dose reduction in cycle 2 then for cycles 3-6 patients will have once weekly CBC with differential and PLT within 24 hours (1 day) (an additional day given for holiday or scheduling) for days 1, 8, 15 (CBC with diff and PLT can be within 3 days of day 1). If patient experienced a dose reduction in cycle 2 (even if drug not reduced until cycle 3) then twice weekly CBC with differential and PLT count must continue for cycle 3 with labs drawn within 24 hours (1 day) (an additional day given for holiday or scheduling) prior to drug administration for dosing decisions (within 3 days for day 1). It is the treating Investigator's discretion to continue with twice weekly CBC with differential and PLT post cycle 3 if deemed necessary (not required). Twice weekly and once weekly labs are required for week off of treatment as well.

[J] Bone marrow biopsy is not required at EOT for patients who are already coming off study for confirmed progression of disease by IMWG criteria.

7.0 RESPONSE ASSESSMENT:

7.1 CRITERIA FOR EVALUATION AND ENDPOINT DEFINITIONS

IMWG Response Criteria 2016

Multiple Myeloma:

For the purpose of establishing one set of criteria for both Phase II and Phase III multiple myeloma studies, the following definitions will be used. These definitions are based on the International Uniform Response Criteria for Multiple Myeloma.

a. **Measurable Disease**: Measurable, quantifiable protein criteria must be present. Acceptable protein criteria are:

- Serum M protein ≥ 1 g/dL (≥ 10 g/L), quantified by using densitometry on serum protein electrophoresis (SPEP).

AND / OR

- Urine M protein [Bence-Jones Protein] ≥ 200 mg/24 hrs (≥ 0.2 g/24 hrs), quantified by 24-hour urine protein electrophoresis

AND / OR

- Bone marrow plasma cells ≥ 30%

OR

- Patients who have both serum M protein levels < 1 g/dL AND urine M protein levels < 200 mg/24 hrs at baseline may be followed by serum free light chain (FLC) assay if involved free light chain level ≥ 10 mg/dL (≥ 100mg/L).

b. **Objective Status via:** www.thelancet.com/oncology Vol 17 August 2016

Response	Criteria
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirate
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis **or** ≥90% reduction in serum M-protein **plus** urine M-protein level <100mg per 24h
Partial response	≥50% reduction of serum M-protein **plus**

	reduction in 24 h urinary M-protein by ≥90% or to < 200mg per 24h; If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, a > 50% reduction in plasma cells is required in place of M-protein. Provided baseline bone marrow plasma-cell percentage was ≥ 30%. In addition to these criteria, if present at baseline, a > 50% reduction in the size (SPD) §§ of soft tissue plasmacytomas is also required.
Minimal response	≥25% but ≤49% reduction of serum M-protein **and** reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL);

	In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defi ned as a 50% (and ≥1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcaemia (>11 mg/dL); Decrease in haemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia see above)
Relapse from MRD negative (to be used	Any one or more of the following criteria:

only if the end point is disease-free survival) **MRD= minimal residual disease**	Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia)

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid haemodilution. IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anaemia, lytic bone lesions. FCM=flow cytometry. SUV_{max}=maximum standardised uptake value. MFC=multiparameter flow cytometry. ^{19}F-FDG PET= ^{19}F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.

*All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (eg, after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

†Sustained MRD negativity when reported should also annotate the method used (eg, sustained flow MRD-negative, sustained sequencing MRD-negative).

‡Bone marrow MFC should follow NGF guidelines. [15] (Paiva, B, Gutierrez, NC, Rosinol, L..., for the GEM (Grupo Español de MM), and PETHEMA (Programa para el Estudio de la Terapéutica en Hemopatías Malignas) Cooperative Study Groups. High-risk cytogenetics and persistent minimal residual disease by multiparameter flow cytometry predict unsustained complete response after autologous stem cell transplantation in multiple myeloma. Blood. 2012; 119: 687–691).

The reference NGF method is an eight-colour two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-colour technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-colour method is most efficient using a lyophilised mixture of antibodies which reduces errors, time, and costs. 5 million

cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

§DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

¶Criteria used by Zamagni and colleagues, [17] (Zamagni, E, Nanni, C, Mancuso, K et al. PET/CT improves the definition of complete response and allows to detect otherwise unidentifiable skeletal progression in multiple myeloma. Clin Cancer Res. 2015; 21: 4384–4390).See all References 17 and expert panel (IMPetUs; Italian Myeloma criteria for PET Use). [16] (Usmani, SZ, Mitchell, A, Waheed, S et al. Prognostic implications of serial 18-fluoro-deoxyglucose emission tomography in multiple myeloma treated with total therapy 3. Blood. 2013; 121: 1819–1823).
See all References , [18] (Nanni, C, Zamagni, E, Versari, A et al. Image interpretation criteria for FDG PET/CT in multiple myeloma: a new proposal from an Italian expert panel. IMPeTUs (Italian Myeloma criteria for PET USe). Eur J Nucl Med Mol Imaging. 2015; 43: 414–421)

See all References Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUV_{max}=2·5 within osteolytic CT areas >1 cm in size, or SUV_{max}=1·5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

‖Derived from international uniform response criteria for multiple myeloma. [13] (Durie, BG, Harousseau, JL, Miguel, JS..., and for the International Myeloma Working Group. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20: 1467–1473)

See all References 13 Minor response definition and clarifications derived from Rajkumar and colleagues. [14] (Rajkumar, SV, Harousseau, JL, Durie, B., and for the International Myeloma Workshop Consensus Panel 1. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011; 117: 4691–4695)

See all References [14] When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. **Bone marrow assessments do not need to be confirmed**. **Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed.** The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

**All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

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

‡‡Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumour size will be determined by the SPD.

¶¶Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

‖‖In the case where a value is felt to be a spurious result per physician discretion (eg, a possible laboratory error), that value will not be considered when determining the lowest value.

7.2 Notes

a. If partial or minimal response rate is an endpoint, patients must have measurable disease at baseline, within the window defined by the study protocol; if multiple measurements are available, the measurement closest to cycle 1, day 1 will be used as baseline •
b. If patients do not have measurable disease at baseline they can only be assessed for at least a complete response or progressive disease
c. In general, the following considerations will allow a more uniform assessment:
   - ï • In the context of a clinical trial, missing serum or urine electrophoresis, or both, can only be accepted at the discretion of an independent review committee
   - ï • If the immunofixation of the serum or urine is negative at baseline, any lack of follow-up testing of the serum or urine can be accepted at the discretion of the independent review committee
   - ï • Parameters that are considered measurable at baseline (serum and urine, FLC if both serum and urine are not measurable) should be performed at each assessment
   - ï **• Urine M-protein is not needed to document partial response or minor response if baseline urine M-protein was not measurable; however, it is still required for complete response and very good partial response**
d. A plasmacytoma that has been radiated is not suitable for response assessment; however, it must be monitored to assess for progressive disease

e. For patients achieving very good partial response by other criteria, a soft tissue plasmacytoma must decrease by more than 90% in the sum of the maximal perpendicular diameter (SPD) compared with baseline
f. Single discrepant results can be ignored at the discretion of an independent review committee
g. For IgA and IgD myelomas, quantitative immunoglobulin measurements are preferred for disease assessments; the same percentage changes applies as for serum M-spike
h. Serum FLC levels should only be used for response assessment when both the serum and urine M-component levels are deemed not measurable
i. **Documentation of response requires two consecutive readings of the applicable disease parameter (serum M-protein, urine M-protein, or serum FLC), performed at any time (no minimum interval is required, it can be done the same day); however, to confirm response, two discrete samples are required; testing cannot be based upon the splitting of a single sample**
j. Whenever more than one parameter is used to assess response, the overall assigned level of response is determined by the lower or lowest level of response
k. Patients should be categorised as stable disease until they meet criteria for any response category or have progressive disease
l. Patients will continue in the last confirmed response category until there is confirmation of progression or improvement to a higher response status; patients cannot move to a lower response category
m. If alternate therapy is started before confirming progressive disease any additional testing during subsequent therapy can be used to confirm progressive disease
n. The lowest confirmed value before suspected progression will be used as baseline for calculation of progression; if a serum and/or urine spike is considered too low to quantitate, this value can be assigned as zero as a baseline for documentation of subsequent progressive disease
o. Any soft tissue plasmacytoma documented at baseline must undergo serial monitoring; otherwise, the patient is classified as inevaluable
p. **Patients will be considered to have progressive disease if they meet the criteria for progression by a variable that was not considered measurable at baseline; however, for patients who had a measurable serum or urine M-spike at baseline, progression cannot be defined by increases in serum FLC alone**
q. In patients with two monoclonal protein bands at the start of therapy, the sum of the two spikes should be used for monitoring of disease
r. Careful attention should be given to new positive immunofixation results appearing in patients who have achieved a complete response, when the isotype is different, it probably represents oligoclonal immune reconstitution and should not be confused with relapse; these bands typically disappear over time FLC=free light chain. IMWG=International Myeloma Working Group.

7.3 Best Response

This is calculated from a sequence of Objective Status evaluations.

Stringent Complete Response (sCR): An objective status of Stringent Complete Response on at least two sequential disease assessments. Only one bone marrow biopsy, done during one of these two disease assessments, is required to confirm the response.

Complete Response (CR): An objective status of Complete Response on at least two sequential disease assessments. Only one bone marrow biopsy, done during one of these two disease assessments, is required to confirm the response.Very Good Partial Response (VGPR): An objective status of Very Good Partial Response on at least two sequential disease assessments.

Partial Response (PR): An objective status of Partial Response on at least two sequential disease

assessments.

Unconfirmed sCR (UsCR): One objective status of Stringent Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed CR (UCR): One objective status of Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed VGPR (UVGPR): One objective status of Very Good Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed PR (UPR): One objective status of Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Stable / No Response (STA): At least one objective status of Stable at least three weeks after registration, but not qualifying as any of the above. If radiographic studies were performed there should be no known progressive or new bone lesions.

Increasing Disease (lNC): First objective status recorded (other than Unknowns or those before three weeks) of Progression, provided this occurs within eight weeks of registration.

Inadequate Assessment Response Unknown (NASS): Progression greater than eight weeks after registration and either all objective statuses prior to registration are unknown or the only known objective statuses occurred less than three weeks after registration.

7.4 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

7.5 Progression-Free Survival

From date of registration to date of first documentation of progression or death due to any cause. Patients last known to be alive and progression-free are censored at date of last contact.

8.0 PHARMACEUTICAL INFORMATION

8.1 Ixazomib

8.1.1 Ixazomib Capsules

Ixazomib is provided in strengths of 4.0-, 3.0-, and 2.3-mg and 2.0-, 0.5-, and 0.2 mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described 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
2.0 mg	Size 2	Swedish orange
0.5 mg	Size 3	Dark green
0.2 mg	Size 4	White opaque

8.1.2 Preparation, Reconstitution, and Dispensing

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

8.1.3 Packaging and Labeling

The study drug ixazomib capsules will be provided by Millennium. The study drug 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.

8.1.4 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. The container should be stored at the investigative site refrigerated. Do not store above 25°C. Do not freeze. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

Ixazomib capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should

be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated and should be informed to not store drug above 25 °C and not to freeze the drug. for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

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

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

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

8.1.5 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 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.

8.1.6 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.

8.1.7 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 the table below:

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)
Anaemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)

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 (%)
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 in the table below. Note that in combination trials, related is defined as related to any study drug in the combination regimen.

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)

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 (%)
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)

1/23/15 approved Millennium, FDA IND 4/8/15, 4/15/15, 5/1/15, 5/4/15, 6/4/15, Amendment # 1 8/17/15, Amendment # 2 9/2/15, Amendment # 3 9/25/15, Amendment # 4 11/24/15, Amendment # 5 2/1/2016, Amendment # 6 4/15/16, Amendment # 7 6/1/16, Amendment # 8 8/12/16, Amendment # 9 12/12/16, Amendment # 10 6/2/17, Amendment # 11 2/5/18, Amendment #12 8-7-18, Amendment # 13 12/10/18

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

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

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.

8.1.8 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.

8.1.9 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.

8.1.10 Ixazomib 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.

8.1.11 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact 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.

For Product Complaints,

- Phone: 1-877-TAKEDA7 (1-877-825-3327)
- E-mail: medicalinformation@tpna.com
- FAX: 1-800-247-8860
- Hours: Mon-Fri, 8 a.m. – 6 p.m. ET

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

8.2 CYCLOPHOSPHAMIDE:

8.2.1 Description:

Cyclophosphamide is commercially available in 25 and 50 mg tablets.

8.2.2 Administration:

Tablets should not be cut, chewed or crushed. Patients should be instructed to drink extra fluids. If a dose is missed, patients should be instructed to take a dose as soon as a patient remembers. Cyclophosphamide tablets should be stored in a closed container at room temperature, away from heat, moisture, and direct light.

8.2.3: Mechanism of Action:

Cyclophosphamide is classed as an alkylating agent of the nitrogen mustard type. An activated form of cyclophosphamide, phosphoramide mustard, alkylates or binds with many intracellular molecular structures, including nucleic acids. Its cytotoxic action is primarily due to cross-linking of strands of DNA and RNA, as well as to inhibition of protein synthesis. Cyclophosphamide is a potent immunosuppressant. It also causes marked and persistent inhibition of cholinesterase activity.

8.2.4: Toxicity:

Myelosuppression, hemorrhagic cystitis (patients must be well hydrated before, during, and after treatment and have adequate renal function). Syndrome of inappropriate antidiuretic hormone (SIADH), fatigue, alopecia, anorexia, nausea, vomiting, hyperuricemia, azospermia, amenorrhea, cardiotoxicity (myocardial necrosis) usually at doses higher than those used in this study.

8.2.5 Drug Interactions:

Cyclophosphamide undergoes metabolic activation via cytochrome P450 3A4 in the liver and may potentially interact with any drug affecting the same isoenzyme. Inhibitors of 3A4 (e.g., itraconazole)

could theoretically inhibit activation and inducers of 3A4 (e.g., phenytoin) could theoretically enhance activation of cyclophosphamide to active alkylating species. For the most part, such interactions have not yet been documented clinically.

8.3 DEXAMETHASONE

8.3.1 Formulation:

0.75 mg , 4 mg, 5 mg, 20 mg , 25 mg tablets

8.3.2 Storage and Stability:

Dexamethasone is to be stored at room temperature.

8.3.3 Administration:

For this study, dexamethasone is administered orally.

8.3.4 Supplier:

Dexamethasone is commercially available.

8.3.5 Description

Dexamethasone (Decadron) is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11b, 17, 21-trihydroxy-16a-methyl-pregna-1, 4-diene-3, 20-dione.

8.3.6 Pharmacology

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Dexamethasone is insoluble in water.

8.3.7 Toxicities:

Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

9.0 PATIENT REGISTRATION

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent

Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should be mailed / faxed to:

Brown University Oncology Research Group,
Brown University
Box G-R 001
Providence, RI 02912
Fax: 401-863-3820
Phone: 401-863-3000
BrUOG@brown.edu

All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form. It is required that source documentation be submitted to support all eligibility criteria (inclusion and exclusion) and also the schedule of evaluations table for prior to registration.

10.0 AGENT ACCOUNTABILITY

Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from manufacturer using a Drug Accountability Record Form.

10.1 Treatment Compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study. Drug accountability will be noted.

All drugs will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt drug preparation, and dispensing, including the applicable lot numbers. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

10.2 Study Drug Disposition

See section 8 for details

11.0 ADVERSE DRUG REACTION (ADR) REPORTING

BrUOG considers the SAE reporting period to begin when the subject signs the study specific informed consent.

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4 for grading all adverse events. All appropriate treatment

areas should have access to a copy of the CTCAE version 4. A copy of the CTCAE version 4 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of ixazomib whether or not considered related to ixazomib. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication. All AEs considered related to trial medication will be followed until resolution even if this occurs post-trial.

11.1 Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

Serious adverse event (SAE)

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- death
- is life-threatening
- inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- persistent or significant disability or incapacity,
- congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience**.**

Unexpected adverse event

An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

11.2 Monitoring of Adverse Events and Period of Observation
Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or illness(es).

11.3 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS
Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

Intensity for each adverse event will be scored using CTCAE Version 4. A copy of the CTCAE Version 4 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 4. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

11.3.1 Pregnancies

Pregnancies occurring while the subject is on study drug or within 4 weeks after the subject's last dose of study drug are considered expedited reportable events. If the subject is on study drug, the study drug is to be discontinued immediately. The pregnancy must be reported to the Brown University Oncology Research Group within 24 hours and BrUOG will in turn report to Millennium Pharmacovigilance within 24 hours (1 working day) of being in receipt of the SAE (completed and submitted to BrUOG by the site) , which includes the SAE Pregnancy Form and Medwatch 3500A. Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 90 days of the subject's last dose of IP, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Millennium Pharmacovigilance Drug Safety immediately by facsimile, or other appropriate method (to be done by BrUOG), using the Medwatch3500A form and SAE pregnancy form (MedWatch 3500A and Pregnancy form-to be completed by site).

The Investigator will follow the subject until completion of the pregnancy, and must notify Millennium Pharmacovigilance (by informing BrUOG) of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial report .If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to BrUOG who will then report to Millennium Pharmacovigilance by facsimile within 24 hours (1 working day) of being in receipt of the formal SAE documents from the site).

Any suspected fetal exposure to ixazomib must be reported to BrUOG within 24 hours of being made aware of the event via completed forms who will then report to Millennium Pharmacovigilance within 1 working day of being in receipt of formal SAE materials submitted to BrUOG from the site. The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects to be related to the in utero exposure to the study drug should also be reported. In the case of a live "normal" birth, Millennium Pharmacovigilance should be advised as soon as the information is available.

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

Serious Adverse Event Reporting Procedures
All pregnancies or suspected pregnancies, including suspected fetal exposure or neonatal deaths must be reported to the Brown University Oncology Research Group within 24 hours of being made aware of the event with completed SAE pregnancy form and 3500A form. BrUOG will report all pregnancies to Millennium Pharmacovigilance within 1 working day of being in receipt of the site submitted SAE materials. All other SAEs are to be reported via fax or email to BrUOG within 24 hours of being made aware of the event and the site has 2 business days (from being made aware of the event) to send the written report to BrUOG, who will then send the SAE report to Millennium Pharmacovigilance product safety within 1 working day of receipt of the completed SAE information (sent to BrUOG from the site). All signed amendments or additions must be recorded on an SAE Form and faxed to Millennium Pharmacovigilance.

Millennium Pharmacovigilance Drug Safety Contact Information: (to be reported to by BrUOG)

SAE and Pregnancy Reporting Contact Information
Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

The principal investigator has the obligation to report all serious adverse events to the Brown University Oncology Research Group's (BrUOG) office who in return will report to the FDA, Millennium Pharmacovigilance, and all sites participating in the trial.

11.4 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. 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.

SAEs must be reported to Millennium Pharmacovigilance (or designee) by BrUOG 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). All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of drug, or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first

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). New primary malignancies will be reported to the FDA as SAEs by BrUOG (sites are required to submit new primary malignancies to BrUOG as SAEs who will then report out as per SAE process).

All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

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

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

> **Fatal and Life Threatening SAEs** within 24 hours of BrUOG receiving formal notification and being made aware of the event via completed forms by site (1 calendar day)
>
> **All other serious (non-fatal/non life threatening) events** within 1 calendar day of BrUOG receiving the formal notification and being made aware of the event via completed forms by site

For BrUOG use: See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

BrUOG must fax or email the SAE Form per the timelines above. The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be

determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

- Causality of the event(s): Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

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

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

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

For Comparator Drugs/Secondary Suspects (Concomitant Medications), all serious adverse experiences will be forwarded to the product manufacturer by the investigator.

11.5 Reporting requirements and procedures depend upon:

1. Whether investigational agents are suspected of causing toxicity;
2. Whether the possibility of such a toxicity was reported in the protocol, consent form, or manufacturer's literature (Expected toxicity); and
3. The severity of grade of the toxicity.

Assessing Causality:
Investigators are required to assess whether there is a reasonable possibility that treatment caused or contributed to an adverse event. The following general guidance may be used:

Yes: if the temporal relationship of the clinical event to treatment administration makes a causal relationship possible, and other drugs, therapeutic interventions or underlying conditions do not provide a sufficient explanation for the observed event.

No:if the temporal relationship of the clinical event to treatment administration makes a causal relationship unlikely, or other drugs, therapeutic interventions or underlying conditions provide a sufficient explanation for the observed event.

11.6 Types of Report: For sites:
Telephone report: For SAE's, both initial and follow-up, contact BrUOG Central Office (401) 863-3000 (or via email), immediately upon learning of the event (within 24 hours) so that the office can prepare for the submission.

Written report: Send the copy of the Medwatch 3500A form within 2 business days of being made aware of the event (see below for life threatening or fatal time lines) to the BrUOG Central Office by email, scan or Fax. If the SAE is a pregnancy or suspected pregnancy the Millennium pregnancy form must ALSO be completed as well and submitted with the 3500A.

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Emails: BrUOG@brown.edu

All deaths or life threatening events during treatment or within 30 days following completion of active protocol therapy (drug) must be reported to BrUOG within 1 business day or as soon as the investigator is made aware of the event, regardless of relationship. Any Life threatening or fatal SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period (30 days post last dose of drug) considered to be related to study drug must be reported to BrUOG within 1 business day, who will then report to Millennium Pharmacovigilance (or designee) within 1 calendar day of being in receipt of the site submitted report.

All adverse events and special reporting situations, whether serious or non-serious, related or unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last dose of drug, or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first

MedWatch 3500A Reporting Guidelines:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Patient initials, DOB, study number
- Sex, weight, age
- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- **Description of event, severity, treatment, and outcome, if known**
- Supportive laboratory results and diagnostics inclusive of applicable medical history
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication (please reference each drug for causality)
- All SAEs must be typed
- ****It is required that you put the following numbers on the Medwatch form for tracking:**
    - **BrUOG 299**

A final report to document resolution of the SAE (such as discharge from hospital) is required.

Follow-up information on the SAE may be requested by Millennium.

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible.

Sites are also to include the following information if known: date and time of administration of medications and all concomitant medications, and medical treatment provided.

Follow-up information:
Additional Info maybe added to a previously submitted report by any of the following methods.

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form

Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The subject identifiers are important so that the new information is added to the correct initial report).

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

11.7 BrUOG Responsibility Regarding Reporting:
The BrUOG Central Office will notify by phone and/or fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 4 calendar day after initial receipt of the information. BrUOG will alert Millennium Pharmacovigilance to a SAE within 1 calendar day of being in receipt of the site submitted SAE. SAEs will be reported as an amendment to the IND (if applicable) within 4 calendar days of notification. They will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA(which will be sent to the Medwatch fax line for IND exemption or to the division fax if there is an IND). A copy of the form will be kept by the BrUOG Central Office.

Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to FDA Division fax line that has responsibility for review of IND)

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well

All written Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to Millennium Pharmacovigilance as well as any pregnancy occurring in association with use of a Millennium Pharmacovigilance Product to:

BrUOG will send to: Millennium Pharmacovigilance via Email or fax:

Fax Number: 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

11.8 Safety Reporting for IND Holders
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

All written Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed/emailed to Millennium Pharmacovigilance as well as any pregnancy occurring in association with use of a Millennium Pharmacovigilance Product.

11.9 Adverse event updates/IND safety reports
Millennium shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

b. IND Annual Reports, for IND study only
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Millennium as a supporter of this study as follows.

12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

Extraordinary medical circumstances or withdrawal of consent by the patient: If, at any time, the constraints of this protocol are detrimental to the patient's health, and/or the patient no longer wishes to continue protocol therapy, the patient shall be withdrawn from protocol therapy. Patients will also be withdrawn from study for the following reasons:

1. **Disease Progression: Any patient with disease progression should be removed from study. Details and tumor measurements should be documented on flow sheets.**
2. Patient is unable to tolerate the toxicity resulting from the study treatment, even with optimal supportive care, in the opinion of the Treating Physician. Adverse event(s) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug. The physician feels it is in the best interest of the patient to stop the treatment.
3. Inter current illness that would, in the judgment of the Investigator, affect assessment of clinical status to a significant degree or require discontinuation of study treatment
4. Non protocol chemotherapy or immunotherapy is administered during the study
5. Noncompliance with protocol or treatment—major violation
6. Pregnancies or Suspected Pregnancies(including positive pregnancy test)
7. Patient is lost to follow-up
8. Patient refuses to continue treatment (patient will continue to be followed for disease-free survival and overall survival)
9. Death

In this event notify:

Brown University Oncology Research Group (BrUOG) Central Office,
Phone: (401) 863-3000
Fax: (401) 860-3820

The BrUOG Central Office will in turn notify the Principal Investigator.

***Document the reason(s) for withdrawal on flow sheets. Follow the patient for survival with follow-up forms as dictated by the protocol**

13.0 FOLLOW-UP

All Subjects that discontinue treatment early for any reason as well as patients who complete therapy will be followed for survival (up to 5 years). At treatment discontinuation, subjects will undergo adverse event evaluation and again approximately 30 days post the last dose of study drug. In addition off study evaluations will be done when treatment is discontinued -Section 6.0.

14.0 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. John Reagan, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is supported by Millennium (the makers of ixazomib).

14.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

14.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.

All revisions to the protocol must be provided to Brown University Oncology Research Group, and Millennium . The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and Millennium of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group, and Millennium . If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

14.3 Protocol amendments or changes in study conduct:

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed and approved by Brown University Oncology Research Group, Millennium and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group, and Millennium.

- Examples of amendments requiring such approval
- Increases in drug dose or duration of exposure of subjects
- Significant changes in the study design (e.g. addition or deletion of a control group)
- Increases in the number of invasive procedures
- Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group and Millennium the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology Research Group and Millennium must be notified and the IRB at the center must be informed immediately. Amendments affecting only administrative aspects of the study do not require formal protocol amendments or IRB approval but the IRB must be kept informed of such administrative changes.

Examples of administrative changes not requiring formal protocol amendments and IRB approval include:

- Changes in the staff used to monitor trials (Millennium considers a change in Principal Investigator or the addition of sub-site(s) to be substantial and requires Millennium approval prior to implementation)
- Minor changes in the packaging or labeling of study drug.

15.0 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

15.1 Good Clinical Practice: The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

15.2 Patient Confidentiality: In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

15.3 Protocol Compliance: The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Millennium and the regulatory authority (ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

15.4 On-site Audits: Regulatory authorities, the IEC/IRB and/or Millennium clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

15.5 Drug Accountability: Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Millennium for disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing ixazomib will be treated and disposed of as hazardous waste in accordance with governing regulations.

15.6 Premature Closure of the Study: This study may be prematurely terminated, if, in the opinion of the investigator or Millennium , there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to Millennium .

15.7 Record Retention:

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principal Investigator (John Reagan, M.D.) and Brown University Oncology

Research Group will monitor this study. The case report forms will be monitored for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. Amgen will notify the Principle Investigator if an application is filed.

16.0 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

17.0 STATISTICS

STATISTICAL DESIGN:

Efficacy Assessment:

A response rate of $\geq 80\%$ will be judged as promising for further evaluation. Further evaluation would not be warranted if the response rate were $\leq 50\%$.

Simon's 2 stage (MiniMax) design has been used.

Hypothesis:

Let p be the probability of response for treatment

H0: $p \leq p0$

HA: $p \geq p1$

The null hypothesis that the true response rate will be tested against a one sided alternative. The first response evaluation will be done after accruing 7 patients and once all 7 patients have had their first confirmatory response. All patients must have received at least 2 cycles of treatment and have had a response post cycle 1/pre-cycle 2 and post cycle 2/pre-cycle 3, at a minimum. If a patient does not have a confirmatory response at these two time points, additional time points will need to be assessed until there is a confirmation. If there are 4 or fewer responses, the trial is stopped for early futility. If 5 or more responses are observed in these 7 patients, the trial will continue to accrue until 20 patients in the preferred treatment schedule. If 13 or fewer patients with clinical responses are observed in 20 patients at this stage, the null hypothesis will be accepted and no further investigation of the drug is warranted. If 14 or more patients with responses are observed after 20 treated patients have been entered at the final dose level, then we will conclude that further investigation of the drug is warranted. This design yields a type I error rate of 0.0417 and power of 81% when the true response rate is 80%.

Run-in for safety after 6 patients in each treatment dosing schedule: Completed by the PI and BrUOG on March 3, 2017. No safety issues were found in assessing the first 6 evaluable patients.

A safety run-in will be performed by the Brown University Oncology Research Group and PI after the first 6 evaluable patients of the initial treatment and the dose escalation (twice weekly) portion.

Unacceptable toxicities include:

- Grade 4 Neutropenia lasting > 7 days
- Grade 4 Thrombocytopenia lasting >7 days
- Grade 3 or 4 Peripheral Neuropathy
- Any treatment related grade 4 non-hematologic toxicity.

There will be two different safety analyses performed:

Treatment schedule #1: Once weekly dosing review:

If more than two patients of the first six treated with once weekly dosing (cycle 1) have unacceptable toxicity, as defined above, then the remaining patients, for a total of 20 treated patients, will be treated with a starting dose of Ixazomib at dose -1 and all remaining patients will be treated with once weekly dosing.

If applicable: Treatment schedule # 2: twice weekly dosing:

Similarly, a safety analysis will be performed once 6 patients have moved forward to twice weekly dosing in cycle 2. If more than 2 patients of the first 6 who complete twice weekly dosing (cycle 2) have

unacceptable toxicity, then the twice weekly dosing will be halted and all remaining patients will continue with the once weekly dosing of ixazomib for a total of 20 treated patients.

For treatment schedule #1 patients will be assessed for their once weekly treatment, after 2 months and assessment will be based on all toxicities which occurred during cycle 1. For the second analysis, which may only be done if applicable, and if no unacceptable toxicities are found with once weekly treatment, all 6 patients will be reviewed once they have completed 2 cycles of treatment, the second cycle of which they would have received treatment based on the twice weekly schedule. Assessments will be done for this cohort once the 6 patients have completed 2 full cycles.

All toxicities will be scored based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.

18.0 References

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APPENDIX A

Agreement to Participate in a Research Study And Authorization for Use and Disclosure of Information

Ixazomib, Oral Metronomic Cyclophosphamide and Dexamethasone for First-Line Treatment of Multiple Myeloma: A Phase II Brown University Oncology Group Study.

You are being asked to take part in a research study. All research studies carried out at <INSERT HOSPITAL> are covered by rules of the Federal government as well as rules of the State and <INSERT HOSPITAL> . Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement that states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

Nature and Purpose of the Study

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. John Reagan, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is being financially supported by Millennium Pharmaceuticals, the makers of the drug ixazomib.

You are being asked to take part in this study because you recently were diagnosed with multiple myeloma. Multiple myeloma is a type of cancer that usually affects the blood, bones, and bone marrow. It can cause weakness from low blood counts (anemia), bone pain and fractures, and increased susceptibility to serious infections. A standard treatment for multiple myeloma is a combination of the chemotherapy drugs bortezomib and cyclophosphamide and the steroid dexamethasone. This study will evaluate a similar combination that includes an investigational chemotherapy drug called ixazomib. Ixazomib is an investigational agent that is not approved by the FDA to treat multiple myeloma or any other cancer. We believe ixazomib can work against myeloma cells in the same way as bortezomib, but ixazomib is given in pill form while bortezomib has to be given by vein. Your doctors are studying the activity and side effects of the combination of ixazomib, cyclophosphamide and dexamethasone, all of which are given in pill form, in patients like you with newly diagnosed multiple myeloma. The investigational part of the treatment is the replacement of bortezomib with ixazomib. If you participate in this study all procedures you receive will be part of standard of care for your disease.

How Many People will take part in the Study?

We expect to enroll approximately 20 subjects into this study. The study is sponsored by the Principal investigator, Dr. John Reagan, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study.

Explanation of Procedures

What will happen if I take part in this research study?

If you choose to take part in this study, then you will need the following tests and procedures, to determine if you are eligible to join the study. You would have several of these tests and procedures even if you did not take part in this research study, meaning they are part of your standard of care. Standard of Care Procedures-Screening

- Medical history
- Bone marrow biopsy in which a needle is put into your bone in the pelvis using a local anesthesia. A small piece of the bone is removed (biopsy) to see with a microscope how much myeloma (your cancer) is in the bone marrow.
- X-rays of all your bones to evaluate which bones are involved with myeloma
- Physical examination to include weight, vital signs, performance assessment, toxicity assessment
- Blood tests prior (approximately 3 tablespoons), to include HIV and hepatitis
- If you are a female of childbearing potential, you will have a pregnancy test during your evaluation and prior to each cycle of treatment
- EKG test

Standard of Care Procedures-While on Study:

- Physical exam, to include vitals, weight, performance assessment and toxicity assessment every cycle (cycles 1-6, about every 28 days) then if you remain on treatment for maintenance, approximately every 56 days.
- Blood tests (about 3 tablespoons) twice weekly for 6 months, then every 2 weeks for the next 18 months (if you continue receiving treatment on the study during maintenance).
- If you are a female of childbearing potential, you will have a pregnancy test prior to each cycle of treatment
- Chemotherapy drugs cyclophosphamide and the steroid dexamethasone

Since you are participating in a research study, you will have Research Only Procedures-While on Study

- Receiving Ixazomib (the study drug) in addition to the standard of care drugs

During the 1st Month of Treatment:
One cycle is 28 days. In the first month of treatment you will be instructed to take one ixazomib capsule and 5 tablets of dexamethasone once a week for 3 weeks (on days 1, 8 and 15 of the 28 day cycle). You will also take 1 tablet of cyclophosphamide every day.

During the 2nd through 6th Months of Treatment Once weekly:
One cycle is 28 days. If you experience toxicities and your doctor feels it is in your best interest, in the 2nd through 6th month of treatment (cycles 2, 3, 4, 5, 6) you will be instructed to take one ixazomib capsule and 5 tablets of dexamethasone once a week for 3 weeks (on days 1, 8 and 15 of the 28 day cycle). You will also take 1 tablet of cyclophosphamide every day.

During the 2nd through 6th Months of Treatment Twice weekly:
One cycle is 28 days. If you do not experience toxicities and your doctor feels it is in your best interest in the 2nd through 6th month of treatment (cycles 2, 3, 4, 5, 6) you will be instructed to take one ixazomib capsule and 5 tablets of dexamethasone twice a week for 3 weeks (on days 1, 4, 8, 11 and 15 and 18 of the 28 day cycle). You will also take 1 tablet of cyclophosphamide every day.

Maintenance Treatment - Months 7 -24:
After you have completed the first 6 months of treatment you and your doctors will decide whether it is best for you to stop treatment on this protocol and have an autologous bone marrow or stem cell transplant. Information about this treatment will be explained in a separate document or manner when the time comes. This is not a part of this clinical trial and is standard of care treatment.

If you and your doctors think it is best for you to stay on the treatment of this study (and not have an autologous bone marrow or stem cell transplant), you will be instructed to take one ixazomib, capsule once a week for 3 weeks (on days 1, 8 and 15) every 28 days for about18 months, to complete 2 years of treatment.

You will be given a drug diary to help you track the dates and times you take the study medications.

Additional Information About Ixazomib, Cyclophosphamide and Dexamethasone:

- Ixazomib and cyclophosphamide tablets should not be broken, chewed or crushed. You should drink extra fluids when you are taking these pills. You should also wash your hands after taking ixazomib and cyclophosphamide.
- Store cyclophosphamide and dexamethasone in a closed container at room temperature, away from heat, moisture, and direct light.
- Ixazomib should be stored in the refrigerator.
- Ixazomib: Ixazomib should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules. During once weekly dosing: Missed doses can be taken as soon you remember and within 48hours/2 days of the missed dose, if the next scheduled dose is 72 hours or more away. During twice weekly dosing: Missed doses can be taken as soon you remember and within 24hours/1 day of the missed dose, if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If you vomit after taking a dose, you should not repeat the dose but should resume dosing at the time of the next scheduled dose.
- Cyclophospamide: 1 pill of cyclophosphamide is taken each day. It can be taken whenever it is convenient and it does not matter whether it is taken with food/water or on an empty stomach. If you miss a dose then take a dose as soon as you remember. However, if it is almost time for your next dose, wait until then and take a regular dose.

- Dexamethasone pills are best taken in the morning each day. It is suggested that you take them with food to reduce stomach upset.
- Call your doctor if you have a question about taking ixazomib, cyclophosphamide or dexamethasone.

If you and your doctors feel that it is not in your best interest to continue on study you will come off study at that time.

End of treatment and follow-up:

When finish treatment, you will undergo the following assessments:

- Physical exam to include vitals and weight and performance assessment. Toxicity assessment to check on any side effects you may be experiencing will be done approximately 30 days post your last dose of drug
- Labs: about 3 tablespoons
- Bone marrow biopsy

How long will I be in the study?

After you finish treatment on study, you will be followed by your physician about every 6 months for up to five additional years. You will be followed even if you undergo an autologous bone marrow transplant. During this time vital signs, performance assessments, disease status and survival information will be collected. It is possible that depending on your disease status, labs may be drawn (approximately 3 tablespoons).

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the discontinuation of treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include:

- Ixazomib will be provided by Millennium Pharmaceuticals at no charge. This drug will be paid for by the study and will not be billed to you or your health insurance company.

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study. . Examples are; all study doctor visits, blood tests, pregnancy tests, tablets of cyclophosphamide and dexamethasone, the administration of the Ixazomib (the study drug), administration of all drugs used to reduce side effects from chemotherapy, x-rays, EKG, and bone marrow biopsy.
These services will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance, you will be responsible for those costs.

Contact Information: If you have any questions regarding this study, you may contact your site Principal Investigator, <INSERT NAME AND PHONE NUMBER>

Discomforts and Risks

You may have side effects while on this study. We will monitor everyone in the study for any side effects. Contact your study doctor if you experience a side effect or have any questions about possible side effects.

Side effects may be mild or serious. We may give you medicines to help lessen side effects. Some side effects will go away as soon as you stop taking the drug. In some cases, side effects can be serious, long-lasting, or may never go away. In some cases discomforts may even result in hospitalization or death. Taking part in this study may lead to time away from work.

IXAZOMIB
Based on studies of ixazomib, it is possible to predict some of the discomforts and risks. However, it is possible that ixazomib may cause risks that have not yet been observed in patients.

The following risks might be seen:
LIKELY (> 20% of patients):

- Low platelet count which may increase the chance of bleeding;
- Skin rash which may range from some red areas, small flat spots, or small raised bumps that may or may not be itchy in a few areas or all over the body
- Feeling tired or weak
- Nausea
- Vomiting
- Diarrhea
- Numbness or tingling or pain feelings in hands and feet
- Constipation
- Lowered red cells or anemia which may make you feel tired;
- Lowered white blood cells called neutrophils that may increase your risk of infection and may be associated with fever
- Not feeling like eating
- Electrolyte imbalance (blood chemical imbalance)
- Loss of water from the body (dehydration) because of vomiting and/or loose stools

UNLIKELY (1-20% of patients):

- Kidney problems which could be severe and lead to kidney failure.
- High blood creatinine and renal failure which means your kidneys are having trouble working well; Patients who had lost body water (dehydration) because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis)
- Flu-like symptoms and other upper respiratory tract infections
- Lung infections including pneumonia or pneumonitis
- Chills
- Pain in the abdomen or back
- Swelling or fluid build up in the arms or legs (edema)
- General aches or pains in muscles, joints, bones, or arms and legs or muscle weakness
- Lowered blood pressure that can commonly cause you to feel lightheaded, faint or pass out when you stand up
- Lowered white blood cells called lymphocytes
- Pain (muscular) in extremities

RARE (<1% of patients):

Some discomforts and risks that occur with lesser frequency (<1%) than those mentioned above, should be noted because they are severe, life-threatening or fatal. With limited experience, we do not know if ixazomb causes such problems.

- Severe, life-threatening or deadly conditions that may involve rash, blistering, skin peeling and mouth sores including Stevens Johnson's Syndrome, Toxic Epidermal Necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS syndrome) and pemphigus vulgaris, have been reported in MLN9708 studies when given in combination with other drugs. These rashes are disorders of the immune system, which differ from regular skin rashes and are generally more severe.
- Posterior reversible encephalopathy syndrome has also been reported with ixazomib with a frequency of <1%. This condition affects the brain and may cause headaches, changes in your vision, changes in your mental status, or seizures (fits), but is usually reversible.
- Transverse myelitis, also a rare condition (<1%), is an inflammatory disease causing injury to the spinal cord which has been reported in a patient receiving ixazomib. This condition may cause varying degrees of muscle weakness, reduced movement in legs, changes in the feelings of the toes and feet, unusual muscle tightness, feelings of pain, changes in bowel (constipation) or urinary (loss of control) function or loss of leg movement. In general, recovery may be partial, complete, or not at all but most patients experiencing transverse myelitis have good to fair recovery of symptoms. We do not know whether ixazomib causes transverse myelitis, however, as it happened to a patient receiving ixazomib, we are not able to exclude the possibility that ixazomib may have contributed to transverse myelitis.
- PML is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. PML has been observed rarely (<0.1 %) in patients taking MLN9708. It is not known whether MLN9708 may contribute to the development of PML

The symptoms of PML are diverse because they are related to the location and amount of damage in the brain, and may evolve over the course of several weeks to months. The most prominent symptoms are clumsiness, progressive weakness, and visual, speech, and sometimes personality changes. The progression of neurologic deficits leads to life threatening disability and frequently results in death.

Additionally, it is worth noting that:

- Ixazomib should not be taken if you have ever had an allergic reaction to boron or boron containing products.
- The following side effects may also be a risk with Ixazomib because they have been reported with another proteasome inhibitor, Bortezomib, in patients with diseases requiring this type of treatment, or in patients who receive Ixazomib in combination with other drugs for cancer treatment:
- Reactivation of the herpes virus infection such as herpes zoster (shingles) that can sometimes cause local pain that may last after recovery from the skin rash and does not go away for some time; and
- Rapid death of cancer cells that may let large amounts of the cells into the blood that injures organs, such as kidneys (this is referred to as tumor lysis syndrome). Your study doctor can talk with you about other common side effects with Bortezomib use.
- The more severe but rare side effects seen with Bortezomib, include but are not limited to, worsening of your heart function (congestive heart failure) that may require additional drugs for treatment or hospitalization. This could be serious enough to result in death.
- Disorders that could affect the function of your lung that could be serious enough to result in death,
- Liver failure.
- Other drugs and supplements may affect the way Ixazomib works. Tell your doctor about all drugs and supplements you are taking while you are in this study.

CYCLOPHOSPHAMIDE:

Likely (> 20% of patients)

- Hair loss, although unlikely at this dose.
- Nausea
- Vomiting
- Decrease in the total number of white blood cells or in the number of neutrophils, also called granulocytes, which are a type of white blood cell
- Lack of enough red blood cells (anemia)
- Fatigue or tiredness
- Temporary red discoloration of urine (not blood)
- Diarrhea
- Loss of appetite

Less likely (1-20% of patients)

- Hot flashes
- Constipation
- Loss of appetite
- Taste changes
- Irritation or sores in the lining of the mouth and throat

- Infection
- Decrease in the number of a type of blood cell that helps to clot blood (platelet)
- Irregular heartbeat
- Eye irritation
- Nail changes, including discoloration or peeling; nail loss can happen
- Hardening of the walls of the veins used for chemotherapy
- Increased blood levels of liver enzymes
- Headache
- Joint pain
- Bone pain
- Muscle pain
- Severe infection
- Bladder irritation that causes bleeding

Rare (<1% of patients)

- Decrease in the ability of the heart to pump blood
- Lung problems such as scarring of the lungs that can cause shortness of breath, low levels of oxygen in the blood, and damage that can be permanent

DEXAMETHASONE

Likely (>20% of patients)

- Elevated blood sugar
- Fluid retention with swelling in the legs
- Electrolyte abnormalities
- Fluid in the lungs
- High blood pressure.
- Euphoria (Having a false sense of feeling very good)
- Change in personality
- Difficulty sleeping,
- Making infections worse,
- Muscle weakness,
- Weakening of the bones,
- Inflammation of the pancreas
- Ulcers, weakening of the skin
- Thyroid changes,
- Vision disturbances.
- Itching

Unlikely (1-20% of patients)

- Joint aches.

Rare (<1% of patients)

- Severe allergic reaction

Immunization procedures should not be undertaken in patients on dexamethasone.

RISKS TO THE UNBORN CHILD

Female subjects: We do not know if the study drug ixazomib will affect mother's milk or an unborn child. Therefore, breast-feeding and pregnant women are not allowed to take part in the study. Due to unknown risks and potential harm to the unborn child/ infant, you should not become pregnant or nurse a baby while on this study.

If you are a female and of child bearing potential, you must have a negative pregnancy test prior to enrolling in the study and prior to each treatment cycle.

Unless you cannot have children because of surgery or other medical reasons (you had an effective tubal ligation, or had the ovaries or the uterus removed; or you are post-menopausal), you must use two effective methods of birth control from the time of signing the informed consent form, for the entire study drug treatment period (including interruptions in treatment), and for 90 days after completing study drug treatment. It is strongly recommended that at least one of these two methods be highly effective (see examples below).

Highly effective methods	**Other effective methods (barrier methods)**
Intra-uterine devices (IUD)	Latex or non-latex condom with or without a spermicidal agent
Hormonal (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide; Cervical cap with a spermicide; Sponge with a spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

You must use birth control methods as directed above, unless you completely avoid having heterosexual intercourse.

Male subjects: We do not know if using ixazomib will affect sperm. Therefore, due to potential risk, you should not get your partner pregnant during the study drug treatment period (including interruptions in treatment). Even if you are surgically sterilized (i.e. have had a vasectomy) you must agree to use an appropriate method of barrier contraception (latex or non-latex condom with a spermicidal agent) during the entire study drug treatment period, and for 90 days after completing study drug treatment. Or, you should completely avoid having heterosexual intercourse.

Highly effective methods	**Other effective methods (barrier methods)**
Vasectomy	Latex or non-latex condom with or without a spermicidal agent
	Diaphragm with spermicide; Cervical cap with spermicide; Sponge with spermicide
If one of the highly effective methods cannot be used, using two effective methods at the same time are recommended.	

All subjects (male or female): If you or your partner becomes pregnant during this study, you must tell the study doctor immediately. The doctor will advise you of the possible risks to your unborn child and discuss options for managing the pregnancy with you. For female subjects who become pregnant while on this study, the study drug will be stopped immediately and the pregnancy will be followed until conclusion.

Please initial below to document that you understand and will comply with these requirements to prevent pregnancies while you are being treated on this study:

_____ _____

Initials **Date**

If you do not understand what any of these discomforts and risks mean, please ask the study doctor or study staff to explain these terms to you.

Risk of Secondary Cancers or Leukemia: The chemotherapy drugs ixazomib and cyclophosphamide may increase the risk of other cancers or leukemia (a blood cancer).

Antiemetics (anti-nausea medications): Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction.

You will receive pre-medication to reduce the risk of infusion/injection reactions on your treatment days. Overall, the pre-medications you will be given are well tolerated.

Venipuncture (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests to determine the effects of your treatment and alter the drug dosages if necessary.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Benefits

Taking part in this study may or may not make your health better. While doctors hope that the investigational drug Ixazomib in combination with cyclophosphamide and dexamethasone will be at least as effective as standard of care treatment (with bortezomib, cyclophosphamide and dexamethasone) against myeloma, this is not yet known. While doctors hope that the side effects of the new treatment combination are not too severe, this is not yet known. Doctors do not yet know if this new treatment combination will or will not benefit you. We do know that the information from this study will help doctors learn more about these drugs as a treatment for myeloma. This information could help future cancer patients.

Your participation in this research study may contribute to the development of commercial products from which Millennium Pharmaceuticals, Inc. or others may derive an economic benefit. You will have no rights to any patents or discoveries arising from this research, and you will receive no economic benefit.

Alternative Therapies

What other choices do I have if I do not take part in this study?

- Getting treatment or care for myeloma without being in a study such as receiving the chemotherapy drugs bortezomib, cyclophosphamide, and dexamethasone,
- Treatment with other myeloma drugs such as lenalidomide (Revlimid), thalidomide or melphalan.
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems, and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

If you decide to stop taking study medication (withdraw from study treatment) for any reason, you will be asked to sign a form, called a Follow-Up After Withdrawal Form, indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. We will continue to collect and submit follow-up information unless you indicate that you do not want that information collected. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

You have the right to change your mind at any time regarding follow-up after withdrawal. If you decide to quit the study please tell the head researcher <INSERT NAME AND PHONE NUMBER FOR CONTACT>

Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. John Reagan, the sponsor of the study, nor BrUOG, the coordinating center, have

money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people who take part in research studies you may contact <INSERT CONTACT NAME AND PHONE NUMBER>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies might use, release, or receive such information:

 The researcher and their support staff;

 The study sponsor, BrUOG, The Brown University Oncology Research Group and Millennium Pharmaceuticals (financial study supporter);

 Doctors, nurses, laboratories and others who provide services to you in connection with this study;

 The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;

 The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;

 People who volunteer to be patient advocates or research volunteer protectors;

 Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and

Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.

You have the right to refuse to sign this form and not participate in the research. Your refusal would have no affect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

Additionally, a description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If after you have signed this form you have any questions relating to your rights, please contact <INSERT CONTACT NAME AND PHONE NUMBER>.

For more detail about your privacy rights see the <INSERT HOSPITAL NAME> Joint Privacy Notice which has or will be given to you.

Research authorization for use and disclosure of information.

The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.
We understand that your medical information is very personal and we will work hard to keep it private. If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form.

Understandings and notifications

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be affected.

However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.

If you sign this consent form, you may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to <INSERT CONTACT NAME, ADDRESS, PHONE NUMBER OF SITE PI>

If after you have signed this form you have any questions relating to your rights, please contact <INSERT CONTACT NAME AND PHONE NUMBER>

Uses and releases covered by this authorization (permission)

Who will release, receive, and/or use your information? This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:

- Every research site for this study, including this hospital, and including each site's research staff and medical staff
- Health care providers who provide services to you in connection with this study
- Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol
- The following research sponsors or supporters and the people and companies that they use to oversee, administer, or conduct the research: BrUOG, the group coordinating the study, and Millennium Pharmaceuticals (financial study supporter)
- The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights
- The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study
- Principal Investigator and other Investigators
- Study Coordinator
- Additional members of the Research Team
- The Patient Advocate or Research Volunteer Protector: _____
- Members of the hospital's administrative staff responsible for administering clinical trials and other research activities
- Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)
- Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee
- The members and staff of the hospitals affiliated Privacy Board (if such a board is used)
- Others: _____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

☐ The entire research record and any medical records held by the hospital may be used and released.
☐ The following information: _____

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN SATISFACTORILY ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.

By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the* <INSERT HOSPITAL NAME> *Privacy notice*

_____ _____ _____
Signature of study volunteer/authorized representative* Date and Time when signed

I was present during the consent PROCESS AND signing of this agreement above by the study volunteer or authorized representative

_____ _____
Signature of witness (required if consent is presented orally or at the request of the IRB) Date

I ASSURE THAT I HAVE FULLY EXPLAINED TO THE ABOVE STUDY VOLUNTEER/ AUTHORIZED REPRESENTATIVE, THE NATURE AND PURPOSE, PROCEDURES AND THE POSSIBLE RISK AND POTENTIAL BENEFITS OF THIS RESEARCH STUDY.

_____ _____ _____
Signature of researcher or designate Date and Time when signed
* If signed by agent other than study volunteer, please explain below.

_____

_____
Documentation that a copy of this Informed Consent was given to the research participant is a Federal requirement. Prior to making a copy of the signed and dated Informed Consent please check appropriate box(es) as applicable to indicate copy provided to:

☐ Study Volunteer ☐ Medical Record ☐ Researcher ☐ Other (Specify)

APPENDIX B: Checklist

Ixazomib, Oral Metronomic Cyclophosphamide and Dexamethasone for First-Line Treatment of Multiple Myeloma: A Phase II Brown University Oncology Group Study.

Inclusion Criteria

_____(y/n) Voluntary, signed written informed consent, Date signed_____

_____(y/n) Age ≥ 18 years of age: Age:_____

_____(y/n) Histologically confirmed multiple myeloma according to WHO classification. Pathology report to be sent to BrUOG for confirmation

_____(y/n) Diagnosis of Multiple Myeloma that has not been previously treated (although patients that received emergent steroid and/or local radiation therapy will be permitted to enter the study). Patients can still be on steroids at time of registration and treatment start, but should be on a tapering dose. Details need to be submitted to BrUOG with dates and doses._____(y/n)

_____(y/n)Measureable disease defined as either an elevated serum M-protein, urine M-protein, ≥ 30% bone marrow plasma cells, or serum free light chains per the IMWG criteria. Confirmation to be sent to BrUOG, see section 7 for criteria

_____(y/n) Life expectancy of ≥ 6 months, confirmation per treating investigator required

_____(y/n) Absolute neutrophil count (ANC) ≥ 1,000/mm3 and platelet count ≥ 75,000/mm3. Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study enrollment. If transfusional support provided, please document for submission to BrUOG

ANC: date:_____value:_____

PLT: Date:_____value:_____

_____(y/n) Calculated creatinine clearance ≥ 30 mL/min (based on the Cockcroft-Gault Equation below) also see section 11.2:

For males:

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

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140 - \text{age[years]}) \times \text{weight [kg]}}{72 \times (\text{serum creatinine[mg/dL]})}$$

Creatinine clearance:_____

_____(y/n) ECOG performance status of 0-1.

_____(y/n) Adequate Liver function; AST or ALT < 3.0 x upper limit of normal (ULN); Total bilirubin <1.5x ULN:

AST:_____ULN:_____//ALT:_____ ULN:_____

T Bili:_____, ULN:_____

_____(y/n) 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.

_____(y/n) Female patients who:

- Are postmenopausal for at least 1 year before the screening visit, OR
- Are surgically sterile, OR

- If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug and obtain a pregnancy test, which must come back negative prior to drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject and obtain a serum pregnancy test, which must come back negative prior to drug. (Periodic abstinence [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Documentation and confirmation of conversations and patient commitment to contraception is required to be noted and sent to BrUOG. Female's menopausal status to be documented and submitted to BrUOG if applicable. Pregnancy test, if applicable, required to be sent to BrUOG.

_____(y/n) Male patients, **even if surgically sterilized** (ie, status post-vasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through *90 days* after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Documentation and confirmation of conversations and patient commitment to contraception is required to be noted and sent to BrUOG.

Exclusion:

_____(y/n) Female patients who are lactating or have a positive serum pregnancy test during the screening period.

_____(y/n) Any surgery within 14 days before enrollment.

_____(y/n) Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.

_____(y/n) Central nervous system involvement.

_____(y/n) Active infection requiring systemic antibiotic therapy or other serious active infection within 7 days before study enrollment (7 day wash-out period post antibiotics)

_____(y/n) Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months

_____(y/n) Systemic treatment, within 14 days before the first dose of ixazomib, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's wort.

_____(y/n) Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive

_____(y/n) Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol. If not applicable, then investigator to document not applicable

_____(y/n) Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. If not applicable, then investigator to document not applicable

_____(y/n) Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing. If not applicable, then investigator to document not applicable

_____(y/n) Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection. No amyloid deposition.

_____(y/n) Patient has ≥ Grade 2 peripheral neuropathy.

_____(y/n) Participation in other clinical trials, including those with other investigational agents not included in this trial, within 30 days of the start of this trial and throughout the duration of this trial.

Please note that source and documentation to be sent to BrUOG for all items in schedule of evaluations table as well

1) Eligibility Form Enclosed __Not Enclosed _____ Not Applicable __
2) Heme/Onc initial note Enclosed __Not Enclosed _____ Not Applicable __
3) Pathology Report(s) Enclosed __Not Enclosed _____ Not Applicable __
4) Skeletal survey Report(s) Enclosed __Not Enclosed _____ Not Applicable __
5) Lab Source Document Enclosed __Not Enclosed _____ Not Applicable __
6) ICF signature page
7) Other documents, please list_____
IRB approval date of protocol: _____
Hospital where patient will be treated with Oncologist: _____

Date patient will begin treatment: _____ Primary Physician: _____

Your signature: _____

APPENDIX C

NCI CTC Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4.0

APPENDIX D

ECOG PATIENT PERFORMANCE STATUS

STATUS	KARNOFSKY	ZUBROD-ECOG-WHO	Description
No complaints	100	0	Normal activity
Able to carry on normal activities	90	1	Symptoms, but fully ambulatory
Normal activity with effort	80		
Cares for self. Unable to carry on normal activity or to do active work	70	2	Symptomatic, but in bed <50% of the day
Requires occasional assistance, but able to care for most of his needs	60		
Requires considerable assistance and frequent medical care	50	3	Needs to be in bed >50% of the day, but not bedridden
Disabled, requires special care and assistance	40		

Severely disabled. Hospitalization indicated though death non imminent	30	4	Unable to get out of bed
Very sick. Hospitalization Necessary. Active support treatment necessary	20		
Moribund	10		
Dead	0		

From: Minna J.D., Higgins G.A and Glapstein E.J. Cancer of the lung: In: DeVita V, Hellman S., Rosenberg S., (Eds.). Cancer: Principles and Practice of Oncology, Lippincott, Philadelphia, 1984, p. 536

APPENDIX E

CASE REPORT FORMS

Attached separately are the BrUOG Case Report Forms