**Mayo Clinic Cancer Center**

# Phase 2 Trial of Pomalidomide, Ixazomib and Dexamethasone in Patients with Multiple Myeloma with Extramedullary Disease or Plasma Cell Leukemia

***Study Chair***: Shaji Kumar MD
Mayo Clinic
200 First Street SW
Rochester, MN 55905
507/284-2511
[redacted]

***Study Co-chairs***: [redacted]

***Statistician***: [redacted]

√Study contributor(s) not responsible for patient care.

MMRC Study: MMRC-052
Celgene Study: PO-MM-PI-002443
Millennium Study: X16025

**Drug Availability**
**Commercial Agents:** Dexamethasone
**Drug Company Supplied:** Ixazomib (***Millennium***), Pomalidomide (***Celgene***)

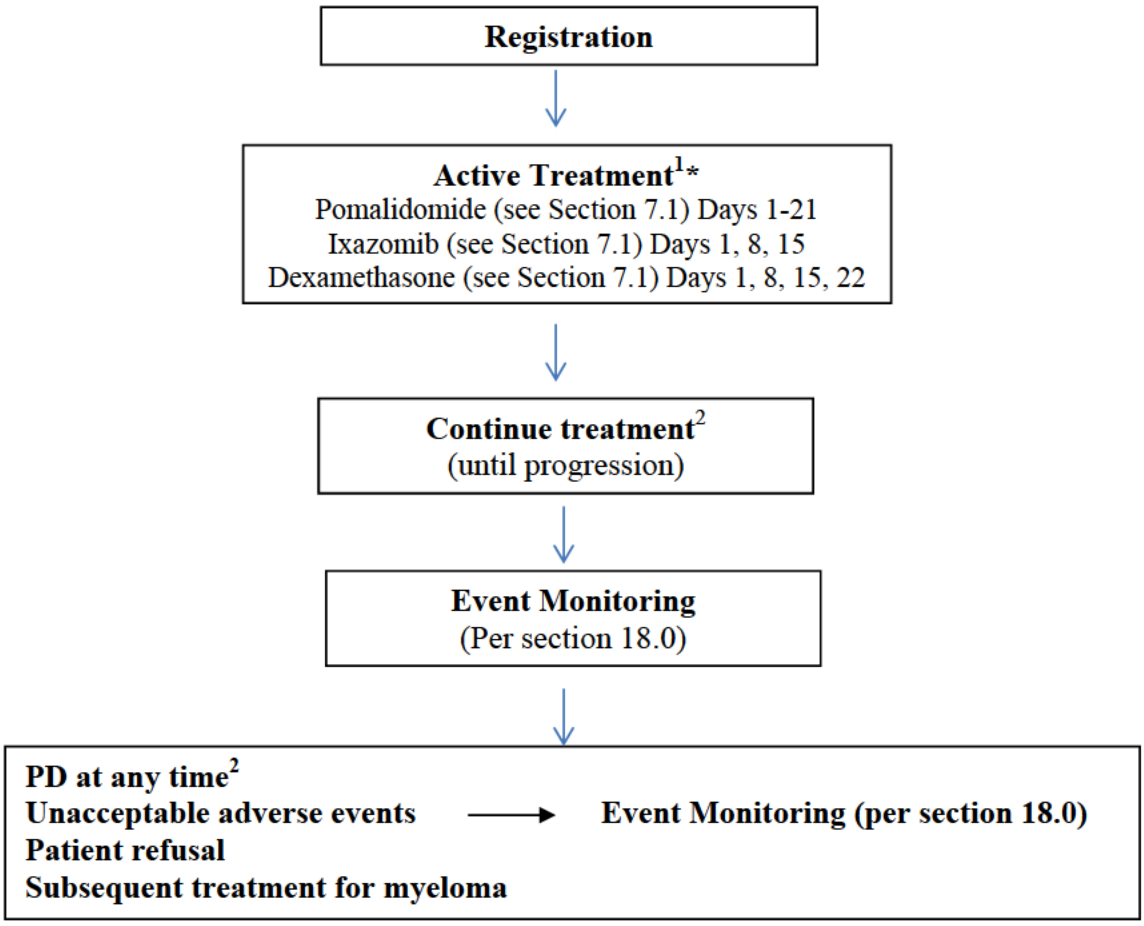
| **Document History** | **(Effective Date)** |
|---|---|
| Activation | December 24, 2015 |
| MCCC Addendum 1 | April 12, 2016 |
| MCCC Addendum 2 | January 11, 2017 |
| MCCC Addendum 3 | August 25, 2017 |
| MCCC Addendum 4 | November 1, 2017 |
| MCCC Addendum 5 | January 10, 2018 |
| MCCC Addendum 6 | December 31, 2019 (ICF update only) |
| MCCC Addendum 7 | April 21, 2020 |

**Protocol Resources**

| Questions: | Contact Name: |
|---|---|
| Patient eligibility*, test schedule, treatment delays/ interruptions/ adjustments, dose modifications, adverse events, data submission, Rave, or patient follow-up | [redacted] |
| Drug administration, nursing guidelines | [redacted] |
| Protocol document, consent form, regulatory issues | [redacted] |
| Adverse Events (paper AdEERS, MedWatch, Non-AER, AML/MDS) | [redacted] |
| Biospecimens resource | [redacted] |

**Table of Contents**

**Schema**




*If a patient is deemed ineligible or a cancel, please refer to Section 13 for follow-up information.

[1] Cycle length = 28 days
[2] Confirmation of PD is not required

| | | |
|---|---|---|
| Generic name: Ixazomib<br>Brand name(s): Ninlaro®<br>Mayo Abbreviation: MLN9708<br>Availability: Millennium | Generic name: Dexamethasone<br>Brand name(s): Decadron®<br>Mayo Abbreviation: DXM<br>Availability: Commercial | Generic name: Pomalidomide<br>Brand name(s): Pomalyst®<br>Mayo Abbreviation: CC4047<br>Availability: Celgene via POMALYST REMS™ program |

## 1.0 Background

1.1 ***Multiple Myeloma:*** Multiple myeloma is a malignancy of the differentiated plasma cells that affect the older patient with a median age at onset of 65-70 years and a slight male predominance. Nearly 20,000 patients with myeloma are diagnosed in the United States each year, and despite considerable improvements in therapy remains incurable and uniformly fatal with a median overall survival of around 8 years. Recent improvements in therapies have significantly improved the survival outcomes, but given the inevitable relapses seen in these patients, new approaches to therapy are clearly needed. The highly effective drug combinations currently used are beset with a degree of toxicity that precludes long-term therapy and also can affect the quality of life metrics. Finally, some of these regimens require IV or subcutaneous administration, which can require frequent clinic, visits for patients. The highly effective multi-drug regimens currently in use typically include a proteasome inhibitor, either bortezomib given IV or SQ or carfilzomib given IV and an IMiD (typically lenalidomide or pomalidomide).

1.2 ***Implications of extramedullary disease in multiple myeloma***: MM is characterized by accumulation of the clonal plasmacytomas (PCs) predominantly in the bone marrow (BM), highlighting the dependence of the tumor on the marrow microenvironment. While all patients with monoclonal gammopathies have some level of circulating plasma cells, development of large numbers of plasma cells in the peripheral blood, referred to as plasma cell leukemia (PCL), has been uncommon.(Kumar et al. 2005) Rarely patients present with solid tumors (solitary or multiple) in the soft tissue and major organs called "extramedullary plasmacytomas" (EMP) or extramedullary disease (EMD). Recently, others and we have observed a disconcerting increase in the incidence of EMD in patients with MM.(Short et al. 2011, Usmani et al. 2012) These patients abruptly develop soft tissue masses, effusions, and plasmacytomas in major organs and the central nervous system.(Rosinol et al. 2004, Madan et al. 2009, Varettoni et al. 2009) Patients with EMD have a poor prognosis, are often difficult to treat, and are refractory to most of the currently available drugs. In fact, development of EMD is associated with a very poor survival in patients with MM. Some studies have suggested that the malignant PCs in EMD have acquired additional genetic changes such as deletion of p53 gene.(Sheth et al. 2009, Lopez-Anglada et al. 2010) The increased occurrence of EMD may also reflect that patients are living longer thus allowing us to observe later stages of natural MM evolution that we were unable to witness in the past. However preliminary data from our studies indicate that this is not the sole explanation; in fact, the increased incidence of EMD may, in part, be related to specific therapies.(Short, Rajkumar et al. 2011) There is an urgent need to develop new treatment approaches for EMD and plasma cell leukemia with new as well as currently available drugs.

We studied a large cohort of 1053 patients with MM seen at Mayo Clinic between January1, 2001, and December 31, 2010, for development of EMD during routine clinical follow up. Among these, 93 patients (8.8%) were identified to have EMD at some point during the disease course, with median time to EMD detection of 11 months (range 0 – 10 years). Patients who developed EMD at any time during the disease course had a shorter overall survival compared with the rest (3.3 vs. 5.2 years, $P < 0.01$). Development of EMD was associated with presence of high-risk FISH abnormalities, especially del17p, elevated serum LDH and high plasma cell labeling index at diagnosis; ($P < 0.05$ for all comparisons). We then studied 174 MM patients with relapsed refractory MM who enrolled on a clinical trial of pomalidomide between 2007-2010, in order to estimate the incidence of EMD in recent years.(Short, Rajkumar et al. 2011) At trial entry, the rate of treatment-emergent EMD was 7.5% (13 of 174 patients). EMD was associated with poor survival; median OS from trial

entry was 16 months with EMP versus not reached, in the rest, P=0.002). Following trial entry, 4 of the 13 patients with EMD responded to treatment. Clearly these studies suggest that tumor cell characteristics at the time of diagnosis that confer the myeloma cell with the ability to survive outside the marrow microenvironment.

1.3 ***Ixazomib***: Ixazomib, which has been formulated for both intravenous (IV) and oral (PO) administration, is a small molecule proteasome inhibitor. It is the citrate ester of the biologically active boronic acid form, MLN2238, which is structurally similar to bortezomib. In water or aqueous systems, ixazomib rapidly hydrolyzes to MLN2238, therefore all doses and concentrations are expressed as MLN2238. Nonclinical studies were conducted with a solution of either MLN2238 or MLN2238 in equilibrium with ixazomib. Similar to bortezomib, MLN2238 potently, reversibly, and selectively inhibits the 20S proteasome. However in contrast to bortezomib, it has a shorter dissociation half-life (t1/2) that may contribute to increased tissue distribution. Bortezomib has a slowly reversible dissociation rate from the red blood cell proteasome, while MLN2238 demonstrates a more rapidly reversible dissociation rate from the blood but sustained effects on bone marrow and tumor proteasomes suggesting better tissue distribution. The pharmacologic implications of this difference in binding kinetics and tissue distribution may in turn result in differences in safety and efficacy profiles in a broader range of tumors. In xenograft-bearing mice, the more rapid dissociation rate correlates with an increased ratio of tumor proteasome inhibition to blood proteasome inhibition, and ixazomib shows greater antitumor activity in several xenograft models, both solid tumor and bortezomib-resistant xenografts, than bortezomib.

<u>*Nonclinical Pharmacology*</u>: MLN2238 refers to the biologically active, boronic acid form of the drug substance, ixazomib. Ixazomib refers to the citrate ester of MLN2238. In water or aqueous systems, the equilibrium shifts from ixazomib to the biologically active boronic acid form MLN2238. All doses and concentrations are expressed as the boronic acid, MLN2238.

<u>In Vitro Pharmacology</u>: MLN2238 preferentially binds the β5 site of the 20S proteasome; at higher concentrations, it also inhibits the activity of the β1 and β2 sites. MLN2238 inhibits ß5 site 20S proteasome activity in vitro, with a half-maximal inhibitory concentration (IC50) of 3.4 nM. Potency is reduced roughly 10-fold versus ß1 (IC50=31 nM) and 1,000-fold versus ß2 (IC50 =3500 nM). MLN2238 was also tested for inhibition against a panel of 103 kinases, 18 receptors (neurotransmitter, ion channel, brain and gut receptors), and 9 serine proteases. In all cases, the IC50 values were >10 μM. MLN2238 and bortezomib have different β5 proteasome dissociation half-lives (t1/2), reflecting differences in their on-off binding kinetics (the β5 proteasome dissociation t1/2 for MLN2238 and bortezomib are 18 and 110 minutes, respectively). Based on these favorable characteristics, ixazomib is anticipated to be effective against multiple myeloma. (Ixazomib Investigator's Brochure (IB). Proteasome inhibition results in the accumulation of poly-ubiquitinated substrates within the cell and leads to cell cycle disruption, with concomitant activation of apoptotic pathways and cell death. Consistent with inhibition of ß5 20S activity, MLN2238 demonstrated potent activity against cultured MDA-MB 231 human breast cancer cells in the WST cell viability assay. In nonclinical models MLN2238 has activity against both solid tumor and bortezomib-resistant xenografts.

<u>*In Vivo Pharmacology*</u>: To determine the activity of MLN2238 in vivo, pharmacodynamic studies were performed in immunocompromised mice bearing either CWR22 human prostate or WSU-DLCL2 (human diffuse large B-cell lymphoma [DLBCL]) tumors. Pharmacodynamic responses in xenograft tumors were analyzed by assessing 20S proteasome inhibition and by evaluating levels of accumulated protein markers such as deoxyribonucleic

acid (DNA) damage-inducible protein 34 (GADD34) and activating transcription factor-3 (ATF-3) as well as measuring growth arrest. Increased expression of GADD34 and ATF-3 is indicative of a downstream biological response to proteasome inhibition. After a single dose of MLN2238, a clear dose response was observed in CWR22 xenografts as seen in both tumor 20S proteasome inhibition and in changes in GADD34 and ATF-3 expression. In WSU-DLCL2 xenografts, greater tumor proteasome inhibition was observed with MLN2238 compared to bortezomib and resulted in increased expression of GADD34 and ATF-3. MLN2238 efficacy experiments demonstrated strong antitumor activity in 4 xenograft models: CWR22 (a human prostate cancer cell line) and 3 human lymphoma cell lines (WSU-DLCL2, OCI-Ly7-7D1-luc, and PHTX-22L). In the case of the CWR22 xenograft model, significant antitumor activity was seen with both IV and PO dosing, demonstrating that this molecule has antitumor activity when administered via different dosing routes. In all 3 lymphoma lines, MLN2238 demonstrated stronger antitumor activity than did bortezomib. In summary, MLN2238, similar to bortezomib, is a dipeptide boronic acid proteasome inhibitor that potently, reversibly, and selectively inhibits the proteasome. There are several features, such as sustained pharmacodynamic effects and activity in a bortezomib-refractory lymphoma xenograft model, that suggest that it may have activity that extends beyond that seen with bortezomib.

*Nonclinical Pharmacokinetics and Pharmacodynamics*: Nonclinical Pharmacokinetics: The pharmacokinetic (PK) properties of MLN2238 were studied in severe combined immunodeficient (SCID) mice bearing human CWR22 tumor xenografts, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Because of the extensive red blood cell (RBC) partitioning of MLN2238, both blood and plasma PK parameters were determined in these studies. MLN2238 had a very low blood clearance (CLb) and a moderate blood volume of distribution at steady-state (Vss,b) after IV administration. The concentration-versus-time curve of MLN2238 displayed a distinct bi-exponential profile with a steep initial distribution phase and a long terminal $t_{1/2}$ (>24 hr) in all species tested. MLN2238 had higher plasma clearance (CLp) and a larger plasma volume of distribution at steady-state (Vss,p) than in blood, largely because of the extensive RBC partitioning. The PK properties of MLN2238 after oral administration were studied in rats and dogs. The plasma oral bioavailability (F) was 41% in rats and nearly 100% in dogs. A clinical prototype formulation of the ixazomib capsule demonstrated that MLN2238 had excellent oral F and an excellent absorption profile in dogs. In addition, interindividual variability, as measured by %CV, in Cmax and $AUC_{0\text{-}24hr}$ after oral administration was low to moderate, similar to that after IV administration. The terminal $t_{1/2}$ after oral administration was also similar to that after IV administration. Comparison of the PK profiles after IV or PO administration in the dog is reported in further detail in the IB. MLN2238 is predicted to have very low CLb (0.0045 L/hr/kg) and a moderate Vss,b (0.79 L/kg) with a long terminal $t_{1/2}$ (>24 hours) in humans. The human efficacious IV dose of MLN2238 is predicted to be 2.0 mg/m$^2$ (0.054 mg/kg) twice weekly. The human efficacious oral dose is predicted to be between 2 and 5 mg/m$^2$ twice weekly, based on a predicted oral F of between 41% (as seen in rats) and 100% (as seen in dogs). The efficacious dose projection for once weekly oral would be higher than twice weekly oral (data not provided).

Metabolism appears to be a major route of elimination for MLN2238 and urinary excretion of the parent drug was negligible (<5% of dose). In vitro in liver microsomes, the metabolism of MLN2238 was high in mice and low to moderate in all other species studied. MLN2238 is metabolized by multiple cytochrome P450 (CYP) isozymes and non-CYP enzymes and proteins. The rank order of relative biotransformation activity of each of the 5 major human

CYP isozymes in the in vivo studies was 3A4 (34.2%) >1A2 (30.7%) >2D6 (14.7%) >2C9 (12.1%) >2C19 (negligible).

MLN2238 is neither an inhibitor of CYP isozymes 1A2, 2C9, 2C19, 2D6, or 3A4 (IC50 >30μM, with an estimated inhibition dissociation constant [Ki] >15μM), nor a time dependent inhibitor of CYP3A4/5 (up to 30 μM). The potential for ixazomib treatment to produce DDIs via CYP inhibition is inferred to be low.

In a Caco-2 cell assay, MLN2238 showed medium permeability with a B-to-A/A-to-B permeability ratio of 2.9. MLN2238 may be a low-affinity substrate of para-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) efflux pump transporters. MLN2238 is not an inhibitor of P-gp, BCRP, and MRP2 (IC50 >100 μM). Consequently, the potential for MLN2238 to cause DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is low.

***Ixazomib Safety Pharmacology***: In exploratory safety pharmacology studies, MLN2238 was a weak inhibitor of the cloned cardiac potassium (K+) human ether à-go-g o related gene (hERG) channel, with an IC50 of 59.6 μM, which exceeds, by approximately 200-fold, the plasma Cmax (111 ng/mL [0.3 μM]) predicted to occur in humans at the optimally efficacious dose after IV administration.

In the GLP-compliant, 1-cycle, repeat-dose, PO toxicology study in beagle dogs, an increase in QTc was seen in male dogs at non-tolerated doses, and a potential increase in QTc was seen in male dogs at tolerated doses. However, increased QTc was not seen in female dogs at any dose, despite the fact that female dogs had plasma Cmax values similar to those of male dogs. Additionally, in a GLP-compliant, 2-cycle, repeat-dose, IV toxicology study in beagle dogs, no increase in QTc was seen in either male or female dogs at any dose, even though dogs in the IV study had higher MLN2238 plasma Cmax values than did the male dogs in the PO study. These data suggest that MLN2238 has a low potential for prolonging the QT interval *in vivo*.

<u>*Toxicology*</u>: All studies discussed in this section were conducted with a solution of either MLN2238 or MLN2238 in equilibrium with ixazomib. Because ixazomib was shown to dissociate immediately to MLN2238 upon exposure to plasma in vitro and therefore could not be detected in plasma samples in vitro all doses, concentrations, and PK parameters noted, here and in the IB, are expressed as the boronic acid, MLN2238.

The toxicology studies of MLN2238 were studied in SCID mice bearing human CWR22 tumor xenografts, Sprague-Dawley rats, beagle dogs, and cynomolgus monkeys. Details of these studies are included in the IB.

<u>*In Vitro* Toxicology</u>: MLN2238 was not mutagenic in a Good Laboratory Practice (GLP)-compliant bacterial reverse mutation assay (Ames assay).

<u>*In Vivo* Toxicology</u>: Details of the *in vivo* toxicology IV dosing and oral dosing studies are provided in the IB. To summarize, the toxicologic effects seen in the IV and PO studies are qualitatively similar to what was previously observed in rodents dosed with bortezomib, for which ixazomib is the next-generation molecule. MLN2238 did not cause significant toxicities that have not been previously observed after dosing with bortezomib. Therefore, on the basis of the similarity in the toxicity profile in rats between MLN22338 and bortezomib, MLN2238 is not known to present any additional safety risks beyond those that occur after

treatment with bortezomib. In addition, there were no significant findings at tolerated exposures in dogs observed after PO administration that were not seen after IV administration, and similar exposures were tolerated regardless of the route of administration.

The potential risks identified from nonclinical studies in dogs and rats include:

- GI toxicity that could result in nausea, vomiting, diarrhea, dehydration, electrolyte imbalance, bleeding, bowel obstruction (including ileus and intussusception), and sepsis.
- Reduced blood counts manifest as thrombocytopenia, neutropenia, and anemia. Reticulocytopenia was described in animals and may be associated with anemia. Reductions in blood counts may predispose to an increased susceptibility to infection, bleeding, and anemia.
- Peripheral nerve ganglia effects that may be associated with peripheral neuropathy that includes pain, burning sensation, and numbness. Autonomic and motor neuropathy may be observed, as both have been reported for bortezomib.
- Lymphoid cell depletion that may be associated with increased risk of infection, including re-activation of herpes zoster.
- Acute phase response that may result in fever and metabolic changes.

All of the effects seen in the GLP-compliant PO toxicology studies in both dogs and rats at tolerated doses were reversible/reversing and can be monitored in the clinic with routine clinical observations (GI disturbances and infections secondary to lymphoid compromise), clinical pathology assessments (inhibition of erythropoiesis, thrombocytopenia, and inflammatory leukogram), and neurologic assessment, as are commonly done for patients treated with bortezomib. The neurologic lesions in these studies are similar to what has been described after treatment with bortezomib and are believed to be the cause of the peripheral neuropathy observed in patients treated with bortezomib.Further details are presented in the IB.

***Clinical Experience with Ixazomib***: Like bortezomib, ixazomib is a small molecule peptide boronic acid analog. Ixazomib is the first investigational proteasome inhibitor with substantial oral bioavailability in patients with multiple myeloma.

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, two phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with lenalidomide (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 are 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 bortezomib 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 ( 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) ( per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate.

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.

***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. 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.(Gupta et al. 2011, Gupta et al. 2012) 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.

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.

***Clinical Trial Experience Using the Oral Formulation of Ixazomib***: As of 27 March 2013, a total of 507 patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma) have been treated in studies evaluating the oral ixazomib formulation. These patients have been treated with different doses of ixazomib either as a single-agent treatment (in 201 patients) or in combination with currently clinically available treatments (in 306 patients). Information regarding the ongoing studies, patient populations, and doses investigated is included in Table 1-1.

**Table 1-1 Clinical Studies of Oral Ixazomib**

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

**Table 1-1 Clinical Studies of Oral Ixazomib**

| Trial/ Population | Description | Doses Investigated |
|---|---|---|
| N = 54 | | |
| **C16010**<br>RRMM<br>N = 200 | PO, W, with LenDex versus placebo-LenDex | 4.0 mg W |
| **C16011**<br>RRAL<br>N = 4 | PO, W, with Dex versus physician's choice of a Dex-based regimen | 4.0 mg W |
| **C16013**<br>RRMM<br>N = 9 | PO, W, with LenDex | 4.0 mg W |
| **C16014**<br>Symptomatic MM<br>N=701 | PO, combination with LenDex | ixazomib 4.0 mg or matching placebo on Days 1, 8, and 15, plus Len 25 mg on Days 1-21 (10 mg if low creatinine clearance, with escalation to 15 mg if tolerated) and Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15, and 22 |
| **C16015**<br>Symptomatic MM with normal renal function or severe renal impairment<br>N=28 | PO, combination with Dex | Part A: ixazomib 3.0 mg on Day 1<br>Part B: ixazomib 4.0 mg on Days 1, 8, and 15, plus Dex 40 mg (or 20 mg if >75 years old) on Days 1, 8, 15 and 22 of a 28-day cycle |
| **C16017**<br>RR follicular lymphoma<br>N=58 | PO, W | 4.0, 5.3, and 7.0 mg, W<br>Treatment at RP2D once determined. |
| **C16018**<br>Advanced solid tumors or hematologic malignancies with varying degrees of liver dysfunction<br>N=45 | Part A: PO, **Day 1 of 15-day cycle**<br>**Part B:** PO, W | **1.5 mg (severe hepatic impairment), 2.3 mg (moderate hepatic impairment), or 4.0 mg (normal hepatic function)** |
| **TB-MC010034**<br>RRMM<br>N = 10 | PO, W | 4.0 mg, W<br>Single agent: 4.0 mg<br>Combination with Rd |

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

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

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

1.4 ***Potential Risks 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 bortezomib, 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 four ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, non-hematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients have been treated with different doses of ixazomib, as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib studies (C16003, C16004, C16007, and C16009) are shown in Table 1-2.

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

| Primary System Organ Class<br>Preferred Term | Oral Single Agent<br>Total n=201 (n%) |
|---|---|
| Subjects with at Least One Adverse Event | 197 (98) |
| Gastrointestinal disorders | 160 (80) |
| Nausea | 106 (53) |
| Diarrhea | 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) |
| Edema 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) |
| Anemia | 42 (21) |
| Neutropenia | 29 (14) |
| Lymphopenia | 20 (10) |
| Skin and subcutaneous tissue disorders | 90 (45) |
| Rash macular[a] | 23 (11) |
| Musculoskeletal and connective tissue disorders | 93 (46) |
| Back pain | 24 (12) |
| Arthralgia | 28 (14) |
| Respiratory, thoracic and mediastinal disorders | 78 (39) |

Table 1-2 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Single-Agent Studies

| Primary System Organ Class<br>Preferred Term | Oral Single Agent<br>Total n=201 (n%) |
|---|---|
| Cough | 28 (14) |
| Dyspnea | 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 two most common terms used to describe rash.

As of 27 March 2013, there are 5 studies actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens. The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, "related" is defined as related to any study drug in the combination regimen.

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

| Primary System Organ Class<br>Preferred Term | Total Oral Combo Agent<br>(5/6/8/13)<br>n = 173 (n%) |
|---|---|
| Subjects with at Least One Adverse Event | 163 (94) |
| Gastrointestinal disorders | 139 (80) |
| Nausea | 65 (38) |
| Diarrhea | 81 (47) |
| Vomiting | 51 (29) |
| Constipation | 57 (33) |
| General disorders and administration site conditions | 132 (76) |
| Fatigue | 76 (44) |
| Pyrexia | 39 (23) |
| Edema 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) |
| Hypokalemia | 34 (20) |
| Blood and lymphatic system disorders | 88 (51) |
| Thrombocytopenia | 49 (28) |
| Anemia | 45 (26) |
| Neutropenia | 43 (25) |
| Lymphopenia | 20 (12) |

Table 1-3 Most Common (At Least 10% of Total) Treatment-Emergent Adverse Events in Oral Combination Studies

| Primary System Organ Class<br>Preferred Term | Total Oral Combo Agent (5/6/8/13)<br>n = 173 (n%) |
|---|---|
| Skin and subcutaneous tissue disorders | 102 (59) |
| Rash maculopapular | 29 (17) |
| Rash macular[a] | 22 (13) |
| Musculoskeletal and connective tissue disorders | 99 (57) |
| Back pain | 42 (24) |
| Pain in extremity | 31 (18) |
| Arthralgia | 22 (13) |
| Respiratory, thoracic and mediastinal disorders | 80 (46) |
| Cough | 36 (21) |
| Dyspnea | 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 two 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, non-Hodgkin's disease, Hodgkin's disease, relapsed and/or refractory multiple myeloma, relapsed or refractory systemic light chain amyloidosis, and newly diagnosed multiple myeloma) to date.(Kumar et al. 2014, Kumar et al. 2014, Kumar et al. 2014, Richardson et al. 2014)

1.5 ***Pomalidomide***: Pomalidomide, a thalidomide analogue, is an immunomodulatory agent that displays similar anti-angiogenic activity, but far greater anti-proliferative and immunomodulatory activity compared to the parent drug. Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC).

The efficacy of pomalidomide in relapsed myeloma has been shown in multiple trials.(Streetly et al. 2008, Lacy et al. 2009, Lacy et al. 2010, Lacy et al. 2011, San Miguel et al. 2013, Leleu et al. 2015) At tolerated doses (MTD=2 mg QD and 5 mg QOD), pomalidomide has been shown to be active in subjects with relapsed or refractory multiple myeloma (MM) (study CC-4047-00-001). In 45 subjects who received doses of pomalidomide ranging, by cohort, up to 10 mg daily, the most commonly occurring dose-limiting toxicity (DLT) was reversible neutropenia. As with other IMiDs administered to

subjects receiving concomitant systemic steroids, deep vein thrombosis (DVT) was seen (in 1subject each in this study and in its subsequent named patient supply rollover program).

Preliminary efficacy and safety data from an ongoing phase II study, led by Martha Lacy, et al, at Mayo Clinic, were published. Sixty patients with relapsed or refractory multiple myeloma were enrolled. Pomalidomide (CC-4047) was given orally at a dose of 2 mg daily on days 1-28 of a 28-day cycle and dexamethasone was given orally at a dose of 40 mg daily on days 1, 8, 15, 22 of each cycle. Patient also received aspirin 325 mg once daily for thromboprophylaxis. The study endpoints were the response rate in patients taking pomalidomide plus dexamethasone including patients with lenalidomide resistant refractory multiple myeloma, and safety of pomalidomide plus dexamethasone. Responses were recorded using the criteria of the International Myeloma Working Group. Thirty eight patients achieved objective response (63%) including CR in 3 patients (5%), VGPR in 17 patients (28%), and PR in 18 patients (30%). The CR + VGPR rate was 33%. Grade 3 or 4 hematologic toxicity occurred in 23 patients (38%); and consisted of anemia in three patients (5%), thrombocytopenia in two patients (3%) and neutropenia in 21 (35%). Among those that developed grade 3/4 neutropenia, all first experienced the neutropenia in cycle 1-3; no new patients experienced grade 3/4 neutropenia in cycle 4 or later. The most common non-hematological grade 3/4 toxicities were fatigue (17%) and pneumonia (8%). Other grade 3/4 non-hematological toxicities that occurred in less than 5% included diarrhea, constipation, hyperglycemia, and neuropathy. One patient (1.6%) had a thromboembolic event of deep vein thrombosis. Lacy et al. have also demonstrated promising clinical activity of pomalidomide in myeloma patients with persistent disease following lenalidomide treatment.

CC-4047-MM-002 is a Celgene sponsored phase 1b/2 multi-center, randomized, open-label, dose escalation study that is evaluating the safety and efficacy of oral pomalidomide alone and in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma. Eligible patients must have received at least 2 prior regimens and all patients must have received prior treatment that includes lenalidomide and bortezomib. This study consists of a phase 1 single agent pomalidomide (maximum tolerated dose [MTD]) segment and phase 2 randomized (pomalidomide plus low-dose dexamethasone versus pomalidomide alone) segment. The MTD was 4 mg 21/28 days (there were 4 drug-related DLTs [Grade 4 neutropenia] at 5 mg). Neutropenia and anemia were the most common grade 3/4 toxicities; there was a dose-dependent increase in grade 4 neutropenia. Based on the preliminary safety and response data, 4 mg 21/28 days is the dose for the phase 2 segment.

Pre-clinical data and the prior experience with thalidomide and lenalidomide in the treatment of patients with myelofibrosis with myeloid metaplasia (MMM) provide the rationale for the use of pomalidomide in patients with MMM. This is further supported by the results of a Celgene sponsored trial (MMM-001) which indicated that pomalidomide therapy at 0.5 mg or 2 mg/day +/- an abbreviated course of prednisone is well tolerated in patients with myelofibrosis and active in the treatment of anemia.

***1.6 Rationale for the current trial***: Clearly patients with EMD and PCL need newer therapies. The combination of pomalidomide and ixazomib provides a potentially powerful combination due to several reasons. We studied 174 consecutive patients with relapsed refractory multiple myeloma (MM) enrolled on a phase II clinical trial of pomalidomide plus low-dose dexamethasone at Mayo Clinic. Extramedullary disease (EMD) was present at the time of trial entry in 7.5% (13 of 174 patients). The response of EMD to pomalidomide plus low-dose dexamethasone included two complete and two partial responses among the 13 patients

(response rate, 31%). The results of this study suggest that pomalidomide can enter the extramedullary sites and attain therapeutic levels, with resultant disease response.

Similar to bortezomib, MLN2238 potently, reversibly, and selectively inhibits the 20S proteasome. However in contrast to bortezomib, it has a shorter dissociation half-life (t1/2) that may contribute to increased tissue distribution. Bortezomib has a slowly reversible dissociation rate from the red blood cell proteasome, while MLN2238 demonstrates a more rapidly reversible dissociation rate from the blood but sustained effects on bone marrow and tumor proteasomes suggesting better tissue distribution. The pharmacologic implications of this difference in binding kinetics and tissue distribution may in turn result in differences in safety and efficacy profiles in a broader range of tumors. In xenograft-bearing mice, the more rapid dissociation rate correlates with an increased ratio of tumor proteasome inhibition to blood proteasome inhibition, and ixazomib shows greater antitumor activity in several xenograft models, both solid tumor and bortezomib-resistant xenografts, than bortezomib. This particular property may enable ixazomib to attain higher levels in the extramedullary compartment, thus offer a particular advantage in this clinical situation. Finally, combinations of an IMiD and a proteasome inhibitor have been the most effective regimens in myeloma, as has been seen with bortezomib or carfilzomib combinations with thalidomide or lenalidomide.

## 2.0 Goals

2.1 Primary

To determine the confirmed response rate (>=PR) of ixazomib, used in combination with pomalidomide and dexamethasone in patients with previously treated multiple myeloma (MM) with extramedullary disease.

2.2 Secondary

2.21 To determine the toxicities associated with ixazomib in combination with pomalidomide and dexamethasone in patients with previously treated MM with extramedullary disease.

2.22 To determine the differential response rates (biochemical versus extramedullary disease) with ixazomib in combination with pomalidomide and dexamethasone in patients with previously treated MM with extramedullary disease.

2.23 To determine the progression free survival following treatment with ixazomib in combination with pomalidomide and dexamethasone in patients with previously treated MM with extramedullary disease.

2.3 Correlative Research

2.31 To assess the proportion of patients achieving minimal residual disease (MRD) negative status.

## 3.0 Patient Eligibility

3.1 Registration - Inclusion Criteria

3.11 Age ≥18 years.

3.12 Previously treated myeloma, currently with extramedullary disease (defined as plasmacytoma outside bone marrow that is not contiguous with a bone lesion) with at least one lesion that has a single diameter of ≥2 cm or plasma cell leukemia (defined as circulating plasma cells exceeding 5% of peripheral blood leukocytes or 0.5 X $10^9$/L or 200 cells/150000 events by flowcytometry).

3.13 The following laboratory values obtained ≤14 days prior to registration.

- Calculated creatinine clearance (using Cockcroft-Gault equation below)* ≥30 mL/min
- Absolute neutrophil count (ANC) ≥1000/$mm^3$
- Platelet count ≥50,000/$mm^3$
- Hemoglobin ≥8.0 g/dL

*Cockcroft-Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age})(\text{actual body weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

$$\text{Creatinine clearance for females} = \frac{(140 - \text{age})(\text{actual body weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

3.14 Patients with measurable disease defined as at least one of the following:

- For patients with EMD measurable disease by CT or MRI or the CT portion of the PET/CT: Must have at least one lesion that has a single diameter of ≥2 cm. Skin lesions can be used if the area is ≥2cm in at least one diameter and measured with a ruler.
- Plasma cell count ≥0.5 X $10^9$/L or 5 percent of the peripheral blood white cells
- Plasma cell count if determined by flow cytometry, ≥200/150,000 events

3.15 ECOG performance status (PS) 0, 1 or 2 (Appendix I).

3.16 Provide informed written consent.

3.17 Negative pregnancy test done ≤7 days prior to registration, for women of childbearing potential only.

3.18 All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.

3.19a Willing to return to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).

3.19b Willing to provide bone marrow and blood samples for correlative research purposes (see Sections 6.12 and 14.1*).*

3.2 Registration - Exclusion Criteria

3.21 Other malignancy requiring active therapy.
EXCEPTIONS: Non-melanoma skin cancer, DCIS or carcinoma-in-situ of the cervix.
NOTE: If there is a history or prior malignancy, they must not be receiving other specific treatment for their cancer.

3.22 Any of the following because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Females of childbearing potential (FCBP)[†] must have a negative serum pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours prior to prescribing pomalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by RevAssist), and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method.
  AT THE SAME TIME, at least 28 days before she starts taking pomalidomide FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.
  See Appendix IV: Pomalidomide Education and Counselling Guidance Document. Patient must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program.
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

3.23 Other co-morbidity which would interfere with patient's ability to participate in trial, e.g. uncontrolled infection, uncompensated heart or lung disease.

3.24 Other concurrent chemotherapy, radiotherapy, or any ancillary therapy considered investigational.
**NOTE:** Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.

3.25 Patient has ≥Grade 3 peripheral neuropathy, or Grade 2 with pain on clinical examination during the screening period.

3.26 Major surgery ≤14 days before study registration.

3.27 Systemic treatment with strong CYP3A4 inducers (e.g. rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, Gingko biloba, St. John's wort) within 7 days before registration.

---

† A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

3.28 Evidence of current uncontrolled cardiovascular conditions, including cardiac arrhythmias, congestive heart failure, angina, or myocardial infarction within the past 6 months. Note: Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.

3.29a QTc >470 milliseconds (msec) on a 12-lead ECG obtained during the Screening period.

Note: If a machine reading is above this value, the ECG should be reviewed by a qualified reader and confirmed on a subsequent ECG.

3.29b Known human immunodeficiency virus (HIV) positive.

3.29c Known hepatitis B surface antigen-positive status, or known or suspected active hepatitis C infection.

3.29d Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

3.29e Known allergy to any of the study medications, their analogues or excipients in the various formulations.

3.29f Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of ixazomib including difficulty swallowing.

3.29g Diarrhea >Grade 1, based on the NCI CTCAE grading, in the absence of antidiarrheals.

**4.0 Test Schedule**

| Tests | Days Prior to Registration ≤30 days | Days Prior to Registration ≤14 days | Day 8, 15, 22 (Cycles 1-3), Day 15 (Cycle 4 onwards)[1] | Every cycle, pre-treatment[1] | End of Cycle 4[1] | End of Treatment (+/-14 days)[1] |
|---|---|---|---|---|---|---|
| Complete medical history | X | | | | | |
| Adverse Event monitoring | | X | | X[16] | | X |
| Physical exam, including weight and vital signs | | X | | X[16] | | X |
| Height | | X | | | | |
| Performance status (ECOG scale) | | X | | X[16] | | X |
| CBC with differential | | X | X | X[16] | | X |
| Chemistry group: sodium, potassium, glucose, alkaline phosphatase; Total and Direct bilirubin; SGOT (AST); serum creatinine, calcium, magnesium | | X | | X[16] | | X |
| LDH, $Beta_2$-microglobulin, C-reactive protein | X | | | | | |
| Electrophoresis of serum and urine (SPEP/UPEP) | | X | | X[3,16] | | X[3] |
| Affected immunoglobulin[2] | | X | | X[2,16] | | X[2] |
| Immunofixation serum and urine | X | | | X[4,16] | | X[4] |
| Immunoglobulin free light chain (MML panel) | | X | | X[5,16] | | X[5] |
| X-ray skeletal survey or low dose full body CT[6] | X | | | X[6] | | X |
| Physical measurement (EMD lesion)[7] | | X | | X | | |
| CT Scan, PET/CT, or MRI for measurement of EMD lesion[8] | X | | | X[8] | | |
| Circulating plasma cell assessment (flow cytometry or peripheral smear)[9] | | X | | X[9,16] | | |
| Bone marrow aspirate and biopsy, myeloma FISH, metaphase cytogenetics, plasma cell proliferation, and flow cytometry | X | | | X[10] | X[10] | X |
| Biopsy of extramedullary lesion[11] | X | | | | | |
| Chest x-ray | X | | | | | |
| Serum pregnancy test[12] | | X[12] | | | | |
| ECG, 12 lead with interpretation | X | | | | | |
| Register patient for POMALYST REMS™ program[13] | | X[13] | | | | |
| Patient Medication Diary (Appendix II)[14] | | | | X | X | X |
| Mandatory tissue block[11] | X | | | | | |
| Mandatory Research Bone marrow sample[R] | X | | | X[10] | | X |
| Mandatory Peripheral Blood sample[R] | X | | | X[15] | | X[15] |

Cycle = 28 days {FOOTNOTES CONTINUE ON NEXT PAGE}

1) All scheduled visits will have a window of ±7 days unless otherwise stated.
   Note: Baseline labs can be used for Cycle 1, Day 1.
2) Affected immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient "non-secretory" or if patient has no heavy chain, i.e. light chain myeloma. Affected immunoglobulin is required after baseline only if it used for disease monitoring instead of SPEP (e.g. IgA myeloma).
3) Urine Electrophoresis required only if used to assess disease response.
4) Immunofixation (IF) needed only in the absence of M-protein to document sCR or CR.
5) Serial light chain required if it is used for disease monitoring (measurable disease at baseline)
6) Skeletal survey/low dose CT not needed at baseline or any other timepoint if PET/CT is done at that timepoint. Otherwise every 365 days (12 months) or more often if clinically indicated.
7) For patients with a clinically palpable lesion.
8) CT or MRI or the CT portion of the PET/CT, same modality should be used at baseline and for serial evaluation. PET/CT scans are required at baseline for all patients with EMD. Assessment of EMD lesions should be performed at end of Cycle 1 and every three cycles or more frequently if clinically indicated. For patients with only skin involvement, skin lesions should be measured with a ruler with images maintained in the medical record.
9) Number of circulating cells may be measured using flow cytometry or peripheral smear as is the standard practice for the institution, but same methodology should be used at every time point. This should be repeated after Cycle 1 and every 2 cycles after that or more often if clinically indicated.
10) At the end of 4 cycles and only required to document CR after that. If a bone marrow was done to confirm CR prior to end of 4 cycles, no further bone marrow examination until the end of treatment.
11) In patients with extramedullary soft tissue disease.
12) For women of childbearing potential only. Must be done ≤7 days prior to registration.
    NOTE: Additional pregnancy testing is required as a condition of participation in the POMALYST REMS™ program.
13) All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program.
14) The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution.
15) At baseline, end of Cycle 4, and at end of treatment. See Section 14.0.
16) Mayo Rochester only: Required evaluations can be done through local facility, phone contact, or by local lab as applicable if patient is unable to return to Mayo facility and is approved by study chair.

R Research funded (see Section 14.0). Will be charged to study and not to patient's account.

4.2 Event Monitoring/Survival Follow-up

| | **Event Monitoring Phase**[1] | | | | |
|---|---|---|---|---|---|
| | q. 3 months until PD | At PD | After PD q. 6 months | Death | New Primary |
| Event Monitoring | X | X | X | X | At each occurrence |

1. If a patient is still alive 3 years after registration, no further follow-up is required.

## 5.0 Grouping Factor: None

## 6.0 Registration Procedures

6.1 Registration Procedures-All Sites

6.11 Mayo Clinic sites:

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the registration/randomization application. The registration/ randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the MCCC web page (http://ccswww.mayo.edu/training/) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [redacted]. If the patient was fully registered, the MCCC Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

6.12 Non Mayo Clinic sites

To register a patient, fax [redacted] a completed eligibility checklist to the Mayo Clinic Cancer Center (MCCC) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.13 (All Sites) Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.2 Verification

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form

- Existence of a signed authorization for use and disclosure of protected health information

6.3 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19b and 14.1).

6.4 Documentation

Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office (fax: 507-284-0885). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.5 Treating institution

Treatment on this protocol must commence under the supervision of the hematologist from the enrolling institution.

6.6 Treatment start

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.7 Pretreatment

Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.8 Baseline symptoms

All required baseline symptoms (see Section 10.62) must be documented and graded.

6.9 Study drug is available on site.

## 7.0 Protocol Treatment

7.1 Treatment Schedule

| Table 7.1 | | | | |
|---|---|---|---|---|
| **Agent** | **Dose Level** | **Route** | **Day** | **Retreatment** |
| Ixazomib | 4 mg | PO | 1, 8, 15 | Every 28 days |
| Pomalidomide | 4 mg | PO | Days 1-21 | Every 28 days |
| Dexamethasone | 40 mg | PO | 1, 8, 15, 22 | Every 28 days |

7.2 Dosing of ixazomib

The doses of ixazomib used in this study are based on data from Millennium's ongoing phase I and II trials, specifically the phase I/II trial of ixazomib (C16005) in combination with lenalidomide and dexamethasone, estimated 4 mg weekly of ixazomib as the RP2D in combination with weekly full dose of lenalidomide (25 mg) and dexamethasone (40 mg).

7.3 How to take ixazomib

The ixazomib should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 240 mL (about 1 cup/8 oz) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers as long as the next scheduled dose is 72 hours or more away. Patients who vomit a dose after ingestion will not receive an additional dose, but should resume dosing at the time of the next scheduled dose.

Drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel.

7.4 Treatment at enrolling institution

A**s of Addendum 7, Mayo Rochester only**

For this protocol, the patient must return to the consenting institution for evaluation at least every third cycle, provided the drug can be sent to the patient and necessary interval evaluations as required by the protocol can be completed remotely or through local healthcare facilities.

MMRC sites:

For this protocol, the patient must return to the consenting institution for evaluation at least every 28 days. Treatment by a local medical doctor (LMD) is not allowed.

7.5 Pomalidomide supply - POMALYST REMS™ program

All patients will be registered to the Celgene POMALYST REMS™ program to obtain pomalidomide, as required by the US Food and Drug Administration (FDA). Patients will receive pomalidomide every 28 days. All unused study drug must be returned to Mayo

Clinic to be recorded. Study drug is to be handed back to the patient to return per POMALYST REMS™ policy. **Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle**. See Appendix IV for pomalidomide information.

## 8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Individual drugs can be dose reduced as per the table below depending on the adverse event attribution. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

**NOTE: If either of pomalidomide or ixazomib is discontinued, the patient can continue on the other drugs, unless specified otherwise in the dose modification tables. If both are discontinued, the patient will go to event monitoring (Section 18.0).**

***ALERT:*** *ADR reporting may be required for some adverse events (See Section 10)*

8.1 Dose Levels for each drug in the combination
(Based on Adverse Events in Tables 8.2-4)

**NOTE: One drug can be reduced each time based on the drug most likely related to the toxicity observed.**

**Table 8.1**

| **Ixazomib (Days 1, 8, 15)** | | **Pomalidomide (Day 1-21)** | | **Dexamethasone (Days 1, 8, 15, 22)** | |
|---|---|---|---|---|---|
| Starting dose | 4 mg | Starting dose | 4 mg | Starting dose | 40 mg |
| -1 | 3 mg | -1 | 3 mg | -1 | 20 mg |
| -2 | 2.3 mg | -2 | 2 mg | -2 | 12 mg |
| -3 | 2.3 mg days 1, 15 | -3 | 1 mg | -3 | 4 mg |
| -4 | Discontinue | -4 | Discontinue | -4 | Discontinue |

If patients cannot tolerate dose level – 3 of ixazomib AND pomalidomide they will go to event monitoring per Section 18.0. If dexamethasone is discontinued, the patient may continue treatment.

8.11 Instruction for initiation of a new cycle of therapy

A new cycle of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥1000/μL
- The platelet count is ≥50,000/μL
- Any other non-hematologic treatment -related adverse event that may have occurred has resolved to ≤Grade 1 or baseline severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of therapy will be held until the toxicity has resolved as described above.

If any drug dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.

If any drug dosing was omitted for the remainder of the previous cycle or if the new cycle is held due to known hematologic toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction. If a new cycle of therapy cannot be restarted within 4 weeks of the scheduled Day 1 due to non-resolution of drug related toxicities, the patient will be removed from protocol therapy and will go to event monitoring.

→ → ***Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified*** ← ←

8.2 Dose modifications for ixazomib based on adverse events during a cycle

**Table 8.2**

| CTCAE System/Organ/Class (SOC) | ADVERSE EVENT | AGENT[#] | ACTION** |
|---|---|---|---|
| Investigations | If platelet count $<30 \times 10^9$/L or ANC $<1.0 \times 10^9$/L or ANC $>1.0 \times 10^9$/L (up to LLN) with fever (temperature >38.5°C) | Ixazomib | Days 2-15: Ixazomib dose should be omitted. Complete blood count (CBC) with differential should be followed weekly. If ANC is $\geq 1.0 \times 10^9$/L and/or platelet counts $\geq 30 \times 10^9$/L, ixazomib may be reinitiated with 1 dose level reduction (see Table 8.1). The subsequent cycle will use the reduced dose. |
| Skin and subcutaneous tissue disorders | Rash, maculopapular, ≥Grade 2 | Ixazomib | Omit ixazomib till rash resolves to ≤Grade 1 (See Section 9.9a). Restart at same dose. If the rash recurs, reduce dose by one dose level. |
| | Any skin, Grade 4 | | Discontinue ixazomib |
| Nervous System Disorders | Newly developed Grade 1 peripheral neuropathy with pain, ≥Grade 2 peripheral neuropathy, | Ixazomib | Reduce dose of ixazomib to the next lower dose level |
| | Grade 2 neuropathy with pain or Grade 3 peripheral neuropathy | Ixazomib | Omit ixazomib until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate ixazomib at the next lower dose level. |

| Table 8.2 | | | |
|---|---|---|---|
| **CTCAE System/Organ/Class (SOC)** | **ADVERSE EVENT** | **AGENT[#]** | **ACTION**** |
| | Grade 4 peripheral neuropathy | Ixazomib | Omit ixazomib.<br>Peripheral neuropathy should be monitored until toxicity resolves or returns to baseline.<br>Upon recovery, if the patient has received clinical benefit from therapy with ixazomib, the investigator may consider restarting ixazomib at the next lower dose level. |
| Other | Any other non-hematological Grade 3 attributable toxicity except:<br>Grade 3 nausea and/or emesis in the absence of optimal anti-emetic prophylaxis<br>Grade 3 diarrhea that occurs in the absence of optimal supportive therapy<br>Grade 3 fatigue | Ixazomib<br>Pomalidomide | Omit ixazomib or pomalidomide or both depending on the attribution to either or both drugs, until resolution to Grade ≤1 or baseline<br>Restart at next lower dose - If a patient is already at the lowest drug level, go to event monitoring<br>If the toxicity can be attributed to either of the drugs, pomalidomide should be discontinued at first instance followed by ixazomib for recurrence of the same toxicity necessitating dose modification |
| | Grade 4 Nonhematologic Toxicities | Ixazomib<br>Pomalidomide | Permanently discontinue pomalidomide.<br>Consider permanently discontinuing ixazomib – Exception if the investigator determines the patient is obtaining a clinical benefit<br>If both ixazomib and pomalidomide are discontinued, the patient will go to event monitoring |

* Located [redacted]

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

**NOTE:** For toxicities attributable to both ixazomib and pomalidomide, only one of the drugs should be reduced for each incidence of toxicity severe enough to necessitate dose reduction. The drug reduced should alternate starting with pomalidomide for the first dose reduction.

**8.3 Dose modifications for pomalidomide based on adverse events during a cycle**

**Table 8.3**

| CTCAE System/Organ/Class (SOC) | ADVERSE EVENT | AGENT | ACTION** |
|---|---|---|---|
| Blood and lymphatic system disorders | Febrile neutropenia associated with fever (≥38.5º C) | Pomalidomide | • Omit pomalidomide dose.<br>• Follow CBC weekly.<br>• If neutropenia has resolved to ≤Grade 2 prior to Day 21 and fever has resolved, restart pomalidomide at next lower dose level and continue the cycle through Day 21<br>• If febrile neutropenia is the only toxicity for which a dose reduction is required G-CSF may be used and the pomalidomide dose maintained |
| Investigations | Grade 3 neutrophil decreased and sustained for 7 days<br>or<br>Grade 4 neutropenia<br><br>Platelet count decreased ≥Grade 3 (platelet count <50,000/mm³) | Pomalidomide | • Omit pomalidomide dose.<br>• Follow CBC weekly.<br>• Hold anticoagulation until platelets ≥50,000/mm³<br>• If platelet count resolves to ≤Grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle through Day 21<br>• If neutropenia has resolved to ≤Grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle through Day 21<br>• If neutropenia is the only toxicity for which a dose reduction is required G-CSF may be used and the pomalidomide dose maintained |
| Skin and subcutaneous tissue disorders | Rash maculopapular Grade 2 or 3 | Pomalidomide | • Omit pomalidomide dose; follow weekly<br>• If the toxicity resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle through Day 21 |
| | Any rash<br>Grade 4 | Pomalidomide | • Discontinue pomalidomide and remove patient from all study treatment |
| Nervous system disorders | Peripheral sensory neuropathy<br>Grade 3 | Pomalidomide | • Omit pomalidomide dose and follow at least weekly<br>• If the toxicity resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle through Day 21 |

| Table 8.3 | | | |
|---|---|---|---|
| **CTCAE System/Organ/Class (SOC)** | **ADVERSE EVENT** | **AGENT** | **ACTION**** |
| | Grade 4 | Pomalidomide | • Discontinue pomalidomide and remove patient from all study treatment |
| Immune system disorders | Allergic reaction Grade 2-3 | Pomalidomide | • Omit dose and follow at least weekly<br>• If the toxicity resolves to ≤Grade 1 prior to Day 15 restart at next lower dose level and continue the cycle until Day 21 |
| | Grade 4 | Pomalidomide | • Discontinue pomalidomide and remove patient from all study treatment |
| Vascular disorders | Thromboembolic event ≥ Grade 3 | Pomalidomide | • Omit dose and start anticoagulation<br>• Restart at investigator's discretion (maintain dose level) |
| Endocrine disorders | Hyperthyroidism or Hypothyroidism ≥ grade 2 | Pomalidomide | • Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy<br>• See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level |
| Other non-hematologic adverse event | Other non-hematologic toxicity ≥ Grade 3 | Pomalidomide | • Omit pomalidomide dose. Follow at least weekly<br>• If the toxicity resolves to ≤Grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle through Day 21 |

* Located at [redacted]

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

**NOTE:** For toxicities attributable to both ixazomib and pomalidomide, only one of the drugs should be reduced for each incidence of toxicity severe enough to necessitate dose reduction. The drug reduced should alternate starting with pomalidomide for the first dose reduction.

**8.4 Dose modifications for dexamethasone based on adverse events during a cycle**

**Table 8.4**

| CTCAE System/Organ/Class (SOC) | ADVERSE EVENT | AGENT | ACTION** |
|---|---|---|---|
| ***BASED ON INTERVAL ADVERSE EVENT (Days 2-28 of each cycle)*** | | | |
| Gastrointestinal disorders | Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL) | Dexamethasone | Treat with H2 blockers, sucralfate, or omeprazole<br>If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level |
| | Dyspepsia, gastric or duodenal ulcer, gastritis ≥Grade 3 (Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self-care ADL; disabling) | Dexamethasone | Omit dexamethasone until symptoms adequately controlled<br>Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole<br>If symptoms persist despite above measures, discontinue dexa-methasone and do not resume<br>Ixazomib and pomalidomide should be continued |
| | Pancreatitis ≥Grade 3 (Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support)) | Dexamethasone | Discontinue dexamethasone and do not resume<br>Ixazomib and pomalidomide should be continued |
| General disorders and administration site conditions | Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca) | Dexamethasone | Diuretics as needed, and decrease dexamethasone dose by 1 dose level<br>If edema persists despite above measures, decrease dose another dose level<br>Discontinue dexamethasone and do not resume if symptoms persist despite second reduction<br>Ixazomib and pomalidomide should be continued |

| Table 8.4 | | | |
|---|---|---|---|
| **CTCAE System/Organ/Class (SOC)** | **ADVERSE EVENT** | **AGENT** | **ACTION**** |
| Psychiatric disorders | Confusion or Mood alteration<br>≥Grade 2 (Severe disorientation; limiting self-care ADL) | Dexamethasone | Omit dexamethasone until symptoms resolve<br>Restart with one dose level reduction<br>If symptoms persist despite above measures, discontinue dexamethasone and do not resume<br>Ixazomib and pomalidomide should be continued |
| Musculoskeletal and connective tissue disorders | Muscle weakness<br>≥ Grade 2<br>Weakness limiting self-care ADL; disabling | Dexamethasone | Decrease dexamethasone dose by one dose level; if weakness persists despite above measures decrease dose by one additional dose level<br>Discontinue dexamethasone and do not resume if symptoms continue to persist<br>Ixazomib and pomalidomide should be continued |
| Metabolism and nutrition disorders | Hyperglycemia<br>Grade 3 or higher (>250 - 500 mg/dL; >13.9 - 27.8 mmol/L); hospitalization indicated | Dexamethasone | Treatment with insulin or oral hypoglycemics as needed<br>If uncontrolled despite above measures, decrease dose by one dose level at a time until levels are satisfactory |

* Located at [redacted]

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

## 9.0 Ancillary Treatment/Supportive Care

9.1 Steroid use

Patients may continue on low level/stable steroid doses for replacement or inhalation therapy.

9.2 Disallowed concurrent treatment

The following treatments are not permitted during the trial:

- Any other investigational treatment
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Any external beam radiotherapy

9.3 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.

9.4 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2932-2947.

9.5 Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals such as loperamide 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. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.6 Renal failure and ixazomib

Two cases of acute renal failure have been reported in patients treated at or above the MTD for intravenous ixazomib (see Section 1.4.3). Volume depletion should be corrected before initiation of study drug. Until further information is available, intake of nonsteroidal anti-inflammatory drugs immediately prior to the administration of ixazomib should be discouraged and requires consultation with the principal investigator. All necessary supportive care consistent with optimal patient care shall be available to patients as necessary.

9.7 Herpes Zoster prophylaxis

Patients may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis with acyclovir 400 mg PO BID is recommended while on study therapy and for 1 month beyond the end of therapy

9.8 Prohibited medications

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 drug-drug interaction with an inducer, MLN2238 exposure would be less - so there is a reduced chance of an adverse event. 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

Extra caution should be exercised when using these medications concomitantly and incidence of any side effects should be carefully monitored. Because these medications are constantly changing, please review any medications for their potential to induce CYP3A4. Potential resources may include the FDA and/or IUPUI websites, or your local institution's pharmacist.

Excluded foods and dietary supplements include St. John's wort and Ginkgo biloba.

9.9a Erythematous Rash with or without Pruritus:

As with bortezomib, rash with or without pruritus has been reported with ixazomib, primarily at the higher doses tested and when given with agents where rash is an overlapping toxicity. The rash may range from limited erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body, to a more generalized eruption that is predominately on the trunk or extremities. Rash has been most commonly characterized as maculopapular or macular. To date, when it does occur, rash is most commonly reported within the first 3 cycles of therapy. The rash is often transient, self-limiting, and is typically Grade 1 to 2 in severity.

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (e.g., prednisone ≤10 mg per day or equivalent) is permitted. Management of a Grade 3 rash may require intravenous antihistamines or corticosteroids. Administration of ixazomib (and/or other causative agent if given in combination) should be modified per protocol and re-initiated at a reduced level from where rash was noted (also, per protocol).

In line with clinical practice, dermatology consult and biopsy of Grade 3 or higher rash or any SAE involving rash is recommended. Prophylactic measures should also be considered if a patient has previously developed a rash (e.g., 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.

9.9b Thrombocytopenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Table 8.2). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

9.9c Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Table 8.2). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

9.9d 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.

9.9e Hypotension

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

9.9f 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.

9.9g 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.

9.9h Thromboprophylaxis

All patients should receive ASA 325 mg daily for thromboprophylaxis. For patients considered high risk for thrombosis, therapeutic anticoagulation with warfarin or low molecular weight heparin should be used.

## 10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

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

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.2 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

**NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.17 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.17 of the protocol.

**NOTE**: "Unexpected adverse experiences" means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:
Definite - The adverse event *is clearly related* to the agent(s).
Probable - The adverse event *is likely related* to the agent(s).
Possible - The adverse event *may be related* to the agent(s).
Unlikely - The adverse event *is doubtfully related* to the agent(s).
Unrelated - The adverse event *is clearly NOT related* to the agent(s).

**Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.**

10.4 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm**

**NOTE:** The combination of an investigational agent with a commercial agent is considered investigational.

**Routine Reporting**

Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.5.

**NOTE:** When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting.

**Expedited Reporting**

An AE that occurs on a combination study must be assessed in accordance with the guidelines for CTEP investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.

An AE that occurs prior to administration of the investigational agent/ intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

Commercial agent expedited reports must be submitted by the Cooperative Group to the FDA via MedWatch.

An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

## 10.41 Special Situations for Expedited Reporting and Submission of Notification Forms

**Exceptions to Expedited Reporting and Submission of Notification Forms: EXPECTED Serious Adverse Events[1]**

An expedited report or notification form may not be required for specific Grade 1, 2, 3 and 4 Serious Adverse Events where the AE is listed in Section 15.0 of the protocol or the consent form* as **EXPECTED**. Any protocol specific reporting procedures MUST BE SPECIFIED BELOW and will **supersede** the standard Expedited Adverse Event Reporting and Notification Form Requirements (Note: These adverse events must still be reported through the routine reporting mechanism [i.e. Nadir/adverse events form]; see footnote 1):

**Table 10.4**

| System Organ Class (SOC) | Adverse event/ Symptoms | CTCAE Grade at which the event will not be expeditedly reported[1]. |
|---|---|---|
| General disorders and administrations site conditions | Fatigue | ≤Grade 3 |
| | | |
| Gastrointestinal | Vomiting | ≤Grade 3 |
| | Nausea | ≤Grade 3 |
| | Diarrhea | ≤Grade 3 |
| Investigations | Neutrophil count decreased | ≤Grade 4 |
| | Platelet count decreased | ≤Grade 4 |
| | Lymphocyte count decreased | ≤Grade 4 |
| | White blood cell count | ≤Grade 4 |
| Blood and lymphatic system disorders | Anemia | ≤Grade 4 |

[1] These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

*The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure.

### 10.411 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

### 10.412 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

**Reportable categories of Death**

- Death attributable to a CTCAE term.
- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring **within 30 days** of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.
- Any death occurring **greater than 30 days** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

### 10.413 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
    - Myelodysplastic syndrome (MDS)
    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

**10.414 Second Malignancy**

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

## 10.42 Expedited Reporting Requirements for IND/IDE Agents

10.421 Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1]

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**

**NOTE:** Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">7 Calendar Days</td><td rowspan="2">24-Hour 3 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>7 Calendar Days</td></tr>
</table>

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.41 of the protocol.

**Expedited AE reporting timelines are defined as:**

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 3 calendar days for:**

- All Grade 4, and Grade 5 AEs

**Expedited 7 calendar day reports for:**

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

### 10.43 Additional instructions:

Special reporting requirements for **Millennium**

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

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

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

Since this is an investigator-initiated study, the principal investigator, Shaji Kumar, 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 also be reported in English to Millennium Pharmacovigilance (or designee):

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

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

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

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

The SAE report must include at minimum:

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

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

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online a [redacted]

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

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

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

**SAE and Pregnancy Reporting Contact Information**

Fax Number: [redacted]

Suggested Reporting Form:

- SAE Report Form (provided by Millennium)
- US FDA MedWatch 3500A: [redacted]
- Any other form deemed appropriate by the sponsor-investigator

**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 Medical Information 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

**Special reporting requirements for Celgene**

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

**Investigator Reporting Responsibilities**
The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports
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 Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Operations
[redacted]

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

**Expedited reporting by investigator to Celgene**
Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document

resolution of the SAE is required. The Celgene tracking number (PO-MM-PI-002443) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

## 10.5 Other Required Reporting

### 10.51 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.43). The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (see Section 10.43). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:
• Pregnancy Report Form

Use form available from the CTEP protocol development page:
[redacted]

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [redacted] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

**Millennium Pharmacovigilance**
Fax Number: [redacted]

### 10.6 Required routine reporting

Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

**Table 10.2**

| SYSTEM ORGAN CLASS | Adverse event/Symptoms | Baseline | Each evaluation |
|---|---|---|---|
| Investigations | Creatinine increased | X | X |
| | Neutrophil count decreased | X | X |
| | Platelet count decreased | X | X |
| General disorders and administration site conditions | Fatigue | X | X |
| Gastrointestinal Disorders | Nausea | X | X |
| | Vomiting | X | X |
| | # of Stools | X | |
| | Diarrhea | | X |
| | Constipation | | X |
| Infections and infestations | Sepsis | X | X |
| Blood and lymphatic system disorders | Febrile neutropenia | X | X |
| Skin and subcutaneous tissue disorders | Rash, maculopapular | X | X |
| Nervous system disorders | Peripheral sensory neuropathy | X | X |
| | Peripheral motor neuropathy | X | X |

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:

10.621 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.622 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.623 Grade 5 AEs (Deaths)

- Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.
- Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

10.63 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

## 11.0 Treatment Evaluation

### 11.1 Terms and definitions

Serum or urine M spike of any level is not a requirement for entry into the study. If present, and meets criteria for measurable disease this will be followed for M protein response using IMWG uniform response criteria as described below.

Definitions for EMD response is similar to those used for patients with lymphoma (Cheson et al. Revised Response Criteria for Malignant Lymphoma). EMD 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 tumor size will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).

Response is based on CT alone or the CT component of PET/CT or MRI where applicable and the PET.

PET/CT scans are required at baseline for all patients with EMD.

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

  Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.
  - M-proteins migrating in the β-region (usually IgA M-proteins)
  - Cases in which the M-spike is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel
  - Cases in which there are multiple peaks of same monoclonal protein (aggregates or dimers)

  If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-spike values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

  Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

- **FLC estimation** is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **CT, PET/CT or MRI** should be performed on all patients with EMD at baseline. This should be repeated after 1 cycle and then every three cycles or more frequently if clinically indicated. The same modality should be used for serial assessment.

- **Peripheral blood testing for circulating plasma cells** should be performed in all patients with plasma cell leukemia at baseline and after 1 cycle and every two cycles thereafter. Peripheral smear or flow cytometry may be used to evaluate circulating plasma cells, but the same modality should be used throughout the study.

- **Response terms:** The following response terms will be used to define M protein response: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD). EMD or PCL response definitions/ criteria are detailed below.

  In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.
  - Serum M-protein ≥1 g/dl
  - Urine M-protein ≥200 mg/24 h
  - Serum FLC assay: Involved FLC level ≥10 mg/dl provided serum FLC ratio is abnormal
  - At least one plasmacytoma that has a single diameter of ≥2 cm.
  - Plasma cell count exceeding 500/microL or 5 percent of the peripheral blood white cells

  The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. ***Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine m-spike) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results*** with the exception of defining stringent complete response.

- **Evaluable disease**: Patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike.

- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-spike or urine M-spike, but has had a detectable monoclonal protein in his/her serum and/or urine and/or measurable serum free light chain.

- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

**Table 11.2**

**Tests Required To Assess M protein Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])**

| On Study Baseline Value | SPEP | 24 hr UPEP[2] | Ig FLC | BM Bx |
|---|---|---|---|---|
| Serum M-spike ≥1 g/dl, and urine M-spike≥200 mg/24 hrs | X | X | | |
| Serum M-spike ≥1 g/dl, but urine M-spike <200 mg/24 hrs | X | | | |
| Serum M-spike<1 g/dl, and urine M-spike≥200 mg/24 hrs | | X | | |
| Serum M-spike <1 g/dl, urine M-spike <200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL | | | X | |

[1] **Immunofixation studies of both serum and urine** are required to document CR regardless of registration values, and in addition **FLC** measurement and **bone marrow immunophenotyping** is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.

[2] For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category

[3] Bone marrow biopsy results do not need to be confirmed (i.e. repeated after documented response).

11.3 Confirmed response

In order to be classified as an M protein response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.
- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2

11.4 Bone progression:

Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.5 Response and Progression:

Criteria for response and progression are listed in Table 11.5. Progressive disease for all patients as defined in Table 11.5. Although the definition for "relapse from CR (or sCR) is listed, this will be documented as a response category in ONLY those protocols evaluating disease free survival.

**Table 11.5**

| CATEGORY | RESPONSE CRITERIA [a] |
|---|---|
| **Stringent complete response (sCR)[e]** | • CR as defined below plus all of the following:<br>• Normal serum FLC ratio<br>• Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [b]<br>• Not applicable for those patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike at baseline |
| **Complete response (CR)** | • Negative immunofixation of the serum and urine<br>• <5% plasma cells in bone marrow<br>• If at on study, the only measurable non-bone marrow parameter was FLC, normalization of FLC ratio<br>• For patients with extramedullary plasmacytoma present at baseline: a) FDG-avid or PET positive prior to therapy: Mass of any size permitted if PET negative and b) Variably FDG-avid or PET negative: Regression to normal size on CT. For patients with only skin involvement, these same criteria apply to skin lesions measured with a ruler.<br>• For patients with plasma cell leukemia at baseline, complete absence of circulating plasma cells |
| **Very good partial response (VGPR)[e]** | • PR as defined below plus all of the following:<br>• Serum and urine M-component detectable by immunofixation but not on electrophoresis or<br>• If at on study, serum measurable, ≥90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h<br>• If at on study, the only measurable non-bone marrow parameter was FLC, ≥90% or greater reduction in the difference between involved and uninvolved free light chain levels<br>• Not applicable for those patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike at baseline |

| Table 11.5 | |
|---|---|
| **CATEGORY** | **RESPONSE CRITERIA [a]** |
| **Partial Response (PR)** | • One of the following:<br>▪ If at on study, serum and urine measurable, a ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h<br>▪ If at on study, only serum measurable (but urine not), a ≥50% reduction of serum M-protein<br>▪ If at on study, urine measurable (but serum not), a reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h<br>▪ If at on study, the only measurable parameter was FLC, a ≥50% decrease in the difference between involved and uninvolved FLC levels<br>▪ For patients with extramedullary plasmacytoma present at baseline: ≥50% decrease in SPD of up to 6 largest dominant masses and a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved sites OR b) Variably FDG-avid or PET negative: regression on CT or by measurements with a ruler in patients with only skin involvement<br>▪ For patients with plasma cell leukemia at baseline, ≥50% reduction in the circulating plasma cell count |
| **Stable disease (SD)** | Not meeting criteria for sCR, CR, VGPR, PR, or progressive disease |
| **Progressive disease (PD) [d]** | Any one or more of the following:<br>• Increase of 25% from lowest value in [f]<br>▪ Serum M-component (absolute increase must be ≥0.5 g/dl)[c]<br>▪ Serum M-component increase ≥1 g/dl, if lowest M component was ≥5 g/dl<br>▪ Urine M-component (absolute increase must be ≥200 mg/24 h) [c]<br>▪ If at on study, the only measurable parameter was FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl) [c]<br>▪ Bone marrow plasma cell percentage (absolute % must be ≥10%)[c]<br>▪ Appearance of a new lesion(s), ≥50% increase from nadir in SPD of more than one lesion, or ≥50% increase in longest diameter of a previous lesion >1 cm in short axis. Lesions PET positive if PET positive prior to therapy<br>▪ ≥50% increase in circulating plasma cells (minimum of 200/mcl)<br>Or any one or more of the following felt related to the underlying clonal plasma cell proliferative disorder<br>▪ Hypercalcemia (≥11.5 mg/dl) if considered related to myeloma<br>▪ Decrease in hemoglobin of ≥2 g/dl if considered related to myeloma<br>▪ Serum creatinine level ≥2 mg/dl if considered related to myeloma |

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy; complete and PR, MR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed.

[b] Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1;2.
[c] Positive immunofixation alone in a patient previously classified as CR will not be considered progression.
[d] Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.
[e] Does not apply to EMD or PCL
[f] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

11.6 Types of Response:

11.61 Biochemical response will be defined as detailed above for serum, urine, and FLC.

11.62 Extramedullary disease response will be defined as detailed above for plasmacytomas and plasma cell leukemia.

**12.0 Descriptive Factors**

12.1 Parameters followed for hematologic response (pick one):.serum M-spike ≥1 g/dL and urine M-spike ≥200 mg/24 hours vs. serum M-spike ≥1g/dL only vs. urine M-spike ≥200 mg/24 hours only vs. serum immunoglobulin free light chain ≥10 mg/dL vs. extramedullary disease only. Distinguish between SPEP measurements versus quantitative IgA measurement for serum M-spike.

12.2 Parameter followed for extramedullary disease: extramedullary plasmacytoma vs. plasma cell leukemia

**13.0 Treatment/Follow–up Decision at Evaluation of Patient**

13.1 Patients who are sCR, CR, VGPR, PR, or SD (or usCR, uCR, uVGPR, uPR) will continue treatment per protocol.

13.2 Patients who develop progressive disease while receiving therapy will go to the event-monitoring phase.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 18.0.

13.4 Criteria for Discontinuation of Treatment
Patients may discontinue treatment for the following reasons:

- Progressive multiple myeloma
- Patient refuses further treatment on the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions)
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation

All attempts should be made to complete the End of Study procedures when the patient discontinues treatment. Patients should go to event monitoring per Section 18.0, unless the patient refuses further study participation or is lost to follow-up.

13.5 Criteria for Study Discontinuation

The study may be temporarily or permanently discontinued at any site and at any time. Reasons for study discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice guidance or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the study is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB.

13.6 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.

If the patient discontinues treatment, the patient will go to the event-monitoring phase of the study (or off study, if applicable):

- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- If the patient never received treatment, on-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

13.7 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in Cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. The patient may continue treatment per protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. If the physician decides treatment should be discontinued, the patient will go directly to the event monitoring phase per section 18.0 and all data up until the point of confirmation of a major violation must be submitted.

13.8 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

## 14.0 Biospecimens

14.1 Summary Table of Research Blood and Biospecimens to be collected for this Protocol

| Correlative Study (See Section 14.4 for more information) | Mandatory or Optional | Blood or Body Fluid being Collected | Type of Collection Tube (color of tube top) | Volume to collect per tube (# of tubes to be collected) | Study Entry | End of cycle 4 | At suspected CR | At EOT | Process at site? (Yes or No) | Temperature Conditions for Storage /Shipping |
|---|---|---|---|---|---|---|---|---|---|---|
| Flow cytometry, GEP | Mandatory | Bone marrow aspirate | EDTA (lavender) | 4 mL (2) | X | X | X | X | No | Cool Pak |
| Flow cytometry for adhesion molecules and circulating myeloma cells | Mandatory | Peripheral blood | EDTA (lavender) | 6 mL (2) | X | X | | X | No | Cool Pak |
| | | | | | | | | | | |
| IHC, FISH | Mandatory[1] | Tissue biopsy block | Paraffin block | (1) | X | | | | No | Ambient |

[1] In patients with extramedullary soft tissue disease

14.2 Collection and Processing

14.21 Bone Marrow and Peripheral Blood for Flow Cytometry

This process will be performed on bone marrow aspirate and on peripheral blood samples following a wash no lyse method on fresh samples.

Draw 8 mL of bone marrow aspirate into two lavender top EDTA tubes. Draw 12 mL of peripheral blood into two lavender top EDTA tubes. It is important to thoroughly mix the samples with the anticoagulant agent by gently inverting the tubes not less than five times.

Samples **are to be collected Monday through Thursday ONLY. Samples are to be shipped the same day they are collected.** Please avoid Friday and holiday collections and shipments.

14.22 Tissue Biopsy Block for Immunohistochemistry

This procedure will be performed on paraffin embedded tissue biopsy sections.

One core of the tissue biopsy (if multiple passes made) or half of the single core should be paraffin embedded and shipped ambient. **NOTE:** Blocks are not expected to be shipped the same day as the bone marrow and peripheral blood collections.

14.3 Shipping and Handling

14.31 Flow cytometry

Immediately ship Cool-Pak via overnight delivery to the address below. A kit will be shipped to the participating site.

Please plan to obtain samples for bone marrow aspirates on Monday through Thursday only.

14.32 Immunohistochemistry

One core of the tissue biopsy (if multiple passes made) or half of the single core should be paraffin embedded and shipped.

14.33 Kits

14.331 **Kits will be used for this study** (except Mayo Clinic in Rochester will use special study cards). Kits will contain supplies and instructions for collection, processing and shipping specimens

14.332 Participating sites may obtain kits by emailing: [redacted] Email requests should include address, contact information and number of kits being requested.

14.333 Kits will be sent via FedEx Ground at no additional cost to participating sites. Allow 3-4 business days to receive kits.

14.34 Shipping

Bone marrow and blood samples can be shipped with Cool Pak the same day they are collected (Monday-Thursday). They should be shipped priority overnight taking care to avoid Friday collection and shipping.

If unavoidable Friday shipping with Saturday delivery can be arranged contacting the laboratory **in advance**.

Please notify Mayo Clinic by email [redacted] or phone [redacted] to notify laboratory when specimens are being shipped.

[redacted]

14.4 Background and Methodology

14.41 Assessment of adhesion molecule profile: We will perform multiparametric flow cytometry on marrow and peripheral blood samples and immunohistochemistry on paraffin embedded samples. In patients with PCL, we will compare the circulating PCs with marrow PCs.

14.42 FISH studies: We will perform FISH studies on paired samples from the EMD as well as BM, examining for the common abnormalities including the IgH translocations, trisomies, p53 deletion, deletion 13 as well as chromosome 1 abnormalities. We hypothesize that p53 abnormalities and acquired abnormalities such as those involving chromosomes 1 and 13 are more likely to be found in the clone in the EMD compared with the clone present in the marrow. We also hypothesize that the genomic instability and clonal evolution form the basis of

increased risk of EMD. Patients with plasma cell leukemia will have FISH performed on the peripheral blood.

14.43 Gene expression profiling: We will perform GEP studies on the EMD tissue and BM samples on all patients who develop EMP and have adequate tissue/cells available. We hypothesize that the PCs in the EMD will exhibit a unique "microenvironment independence" signature suggesting the lack of continued need for the marrow microenvironment. The relative plasma cell gene expression profiles will be analyzed using high-density oligonucleotide microarrays containing probes for 50,000 transcripts and variants including 14,500 known genes (U133 Plus 2.0 array; Affymetrix, Santa Clara, CA). The arrays will be scanned using a Genechip 300 scanner and GeneChip 5.0 software (Affymetrix) will used to quantitatively analyze the scanned image. We have extensive experience with analysis. Functional analysis to determine the biological relevance of the data and to identify novel, dysregulated genes and biological pathways will be performed using a functional annotation and network mapping tool, Ingenuity Systems.

14.44 Microvessel density: We will estimate the microvessel density (MVD) in the paraffin embedded biopsy tissue from EMD as well as BM samples from the time of trial entry and any subsequent samples. We hypothesize that increased BM angiogenesis reflects a plasma cell clone with increased capacity to modulate the microenvironment. We also hypothesize that the EMDs with high MVD will have a poor outcome, as tumor cells are likely more resistant to treatment.

## 15.0 Drug Information

### 15.1 Ixazomib (MLN9708, Ninlaro®)

#### 15.11 Background

Ixazomib (MLN9708) is a second-generation small molecule inhibitor of the 20S proteasome that is under development for the treatment of non-hematologic malignancies, lymphoma, and multiple myeloma.

Ixazomib (MLN2238) refers to the biologically active, boronic acid form of the drug substance, ixazomib citrate (MLN9708). The transition to MLN2238 occurs in any aqueous system.

#### 15.12 Formulation

The ixazomib capsule drug product formulation consists of drug substance, microcrystalline cellulose, talc, and magnesium stearate. Seven different capsule strengths are manufactured: 0.2, 0.5, 2.0, 2.3, 3.0, 4.0, and 5.5 mg; each capsule strength has a unique color. Dosage strength is stated as ixazomib (the active boronic acid). Ixazomib (MLN9708) capsules are individually packaged in blisters.

Matching placebo capsules have been manufactured for the 2.3, 3.0, 4.0, and 5.5 mg ixazomib (MLN9708) capsules. The placebo capsules contain microcrystalline cellulose, talc, and magnesium stearate and are identical in color and size to the corresponding active dose.

#### 15.13 Preparation and storage

Ixazomib (MLN9708) capsules (0.2 mg, 0.5 mg, 2 mg), individually packaged in blisters, can be stored at 2ºC to 8ºC or "Do not store above 25ºC. Do not freeze." Ixazomib capsules (2.3 mg, 3 mg, 4 mg, and 5.5 mg), individually packaged in blisters, can be stored at "2ºC - 8ºC" or "Do not store above 25ºC. Do not freeze."

Ixazomib that is dispensed to the patient for take-home dosing should remain in the blister packaging until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Capsules should remain in the blisters until the point of use. Ixazomib capsules must be administered as intact capsules and must not be opened or manipulated in any way. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients will be instructed to store the medication in the refrigerator until the time of use. Reconciliation will occur accordingly when the patient returns for their next cycle of therapy. Returned unused capsules should be discarded in a proper biohazard container.

Ixazomib is an anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling ixazomib. It is recommended to wear gloves and protective garments during preparation when dispensed in clinic. Please refer to published guidelines regarding the proper handling and disposal of anticancer agents.

#### 15.14 Administration

Ixazomib (MLN9708) capsules must be administered as intact capsules and are not intended to be opened or manipulated in any way. Capsules should be taken on an empty stomach with approximately 8 oz (1 cup) of water at least 1 hour before or at least 2 hours after food.

Ixazomib should not be taken if the patient has had a serious allergic reaction to boron or boron containing products.

15.15 **Pharmacokinetic information**

a) Absorption: After oral dosing, ixazomib is rapidly absorbed with a median $T_{max}$ of 1 hour. The lack of a discernible relationship between BSA and ixazomib clearance over a relatively wide BSA range (1.4-2.6 $m^2$) indicates that total systemic exposure (AUC) following fixed dosing should be independent of the individual patient's BSA. A high-fat meal decreased both the rate and extent of absorption. Therefore, ixazomib should be administered on an empty stomach.

b) Distribution: The steady state volume of distribution is large and is estimated to be 543 L. Ixazomib is 88-94% protein bound.

c) Metabolism: Metabolism is the primary route for elimination of ixazomib by both CYP and non-CYP enzymes. CYP3A4 and 1A2 comprise the major CYP isozymes that contribute to ixazomib metabolism.

d) Excretion: The mean terminal half-life is 9.5 days. Renal elimination is a minor clearance pathway for ixazomib. Dosing adjustment is not required in patients with mild and moderate renal impairment in studies.

However, in a dedicated renal impairment study (C16015), unbound AUC0-last was 38% higher in patients with severe renal impairment or end-stage renal disease (ESRD) requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is recommended in patients with severe renal impairment and ESRD requiring dialysis. Unbound systemic exposures of ixazomib are 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. A reduced starting dose of ixazomib is recommended for patients with moderate or severe hepatic impairment.

15.16 **Potential Drug Interactions**

The PK of ixazomib was similar with and without coadministration of clarithromycin, a strong CYP3A inhibitor, and therefore no dose adjustment is necessary when ixazomib is administered with CYP3A inhibitors. In the population PK analysis, coadministration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Thus, no dose adjustment is required for patients receiving strong CYP1A2 inhibitors. In a clinical rifampin DDI study, ixazomib Cmax and AUC0-last were reduced in the presence of rifampin by approximately 54% and 74%, respectively. As a result, the coadministration of strong CYP3A inducers with ixazomib is not recommended. Ixazomib is neither a time-dependent nor reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5, therefore the potential for ixazomib to produce DDIs via CYP isozyme inhibition is low. Ixazomib did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity. The potential for ixazomib to cause DDIs with substrates or inhibitors of P-gp, BCRP, MRP2, MATE-1, MATE2-K, OCT2, OAT1, OAT3, and OATPs is low.

Pharmacokinetic parameters for ixazomib coadministered with lenalidomide and dexamethasone (LenDex), are similar to those observed when ixazomib is administered as a single agent. This suggests that there is no readily apparent effect of coadministration of lenalidomide and dexamethasone on the clinical PK of ixazomib.

Ixazomib should not be taken if the patient has had a serious allergic reaction to boron or boron containing products.

15.17 **Known potential toxicities**

See the current version of the Investigator's Brochure for more complete information including potential risks, as well as recommendations for clinical monitoring and medical management of toxicity.

**Very common (≥10%):** anemia, neutropenia, thrombocytopenia, constipation, diarrhea, nausea, vomiting, fatigue, decreased appetite, dizziness, peripheral neuropathy
**Common (≥1% to <10%):** Herpes zoster, peripheral sensory neuropathy, erythema, rash, erythematous rash, pruritic rash, macular rash, peripheral edema, upper respiratory tract infection, back pain, maculo-papular rash, popular rash
**Uncommon (≥0.1% to <1%):** generalized pruritis, generalized rash
**Herpes zoster** – antiviral prophylaxis should be considered in patients being treated with ixazomib to decrease the risk of herpes zoster reactivation.
**Rare but serious risks –** intestinal obstruction, pneumonia, life-threatening severe skin rash (Steven Johnson syndrome, TEN, DRESS syndrome), thrombotic thrombocytopenic purpura, tumor lysis syndrome, renal failure, posterior reversible encephalopathy syndrome, transverse myelitis, progressive multifocal leukoencephalopathy.

**Overdose-** There is no known specific antidote for ixazomib overdose. In the event of an overdose in blinded studies, study medication assignment should be unblinded immediately. The clinician should consider admitting the patient to the hospital for IV hydration, monitoring for adverse drug reaction, monitoring of vital signs, and appropriate supportive care. Gavage may be considered, but it should be kept in mind that ixazomib absorption is rapid. Ixazomib is not readily dialyzable.

15.18 **Drug procurement**

Investigational product will be supplied free of charge to trial participants by Millennium Pharmaceuticals, Inc.

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.

15.2 Pomalidomide (Pomalyst®, CC-4047)

Please consult the most current Investigator's Brochure and package insert for complete drug information.

15.21 **Background**: Pomalidomide (CC-4047) is a novel drug in the class of immunomodulatory agents known as IMiDs compounds. Pomalidomide binds to its molecular target cereblon (CRBN), a protein that is part of an E3 ubiquitin ligase complex, which is responsible for the poly-ubiquitination of substrate proteins, targeting them for subcellular redistribution and destruction by the proteasome. The pharmacologic properties of pomalidomide are of potential therapeutic benefit in the treatment of various hematologic neoplasms (such as multiple myeloma and myeloproliferative neoplasm-associated myelofibrosis), non-neoplastic hematologic disorders (such as β-thalassemia and sickle cell disease) and non-hematologic disorders such as systemic sclerosis, as well as solid tumor neoplasms.

15.22 **Formulation**: Pomalidomide (CC-4047) capsules can be 0.5-mg gelatin capsules (size 4 reddish brown), 1-mg hard gelatin capsules (size 4 reddish brown), 2-mg (size 2 reddish-brown), 3-mg and 4-mg hard gelatin capsules (size 2 reddish-brown), and 5-mg hard gelatin capsules (size 1 reddish-brown), containing pomalidomide, mannitol, pregelatinized starch, and sodium stearyl fumarate.

Pomalidomide (CC-4047) capsules are supplied in high density polyethylene (HDPE) containers fitted with induction seals and child-resistant plastic closures or PVC/PCTFE blister with push-through foil.

15.23 **Preparation and storage**: Store drug at controlled room temperature, between 68-77 ºF (20-25ºC) or as indicated on the manufacturer's label. The expiration date is indicated on the label.

Only enough study drug for one cycle of therapy (one month) may be dispensed.

15.24 **Administration:** Pomalidomide is administered by mouth at approximately the same time each day with water. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal. Capsules should be swallowed whole, and should not be broken, chewed or opened. If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up. Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment. Patients who take more than the prescribed dose of pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

15.25 **Pharmacokinetic information**:
a) Absorption – oral absorption has been moderately rapid with first dose- Cmax occurring in 1.5 to 4 hrs. More than 70% of the pomalidomide dose is absorbed in humans. A high fat meal decreased the rate of absorption but had minimal effect on overall extent of absorption; therefore drug may be administered without regard to food intake.
b) Distribution – Apparent volume of distribution in healthy subjects ranged from 74-138 L across a dose range of 1 to 10 mg daily. Pomalidomide protein binding in human plasma is low to moderate (15.8% for R-enantiomer, 42.2% for S-enantiomer) and the binding is concentration independent in the concentration range of 30 and 1000 ng/mL. Drug distributes into semen.

c) Metabolism - Eight metabolites were detected in plasma, each at exposures <10% of the plasma pomalidomide. CYP-dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non-CYP dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%.
d) Excretion – In healthy patients, 72.8% of the dose was recovered in urine and 15.5% was recovered in feces. Less than 3 % of the dose is excreted as unchanged pomalidomide in the urine. The geometric mean terminal elimination was approximately 7.5 hours.

15.26 **Potential Drug Interactions**: Pomalidomide is partially metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp).

Coadministration of pomalidomide with the strong CYP3A4/5 and P-gp inhibitor ketoconazole, or the strong CYP3A4/5 inducer carbamazepine, had no clinically relevant effect on exposure to pomalidomide. Coadministration of the strong CYP1A2 inhibitor fluvoxamine with pomalidomide increased mean exposure to pomalidomide by 125% compared to pomalidomide alone. If strong inhibitors of CYP1A2 are coadministered with pomalidomide, the pomalidomide dose by should be reduced 50%.

Smoking: Administration of pomalidomide in smokers, with smoking tobacco known to induce the CYP1A2 isoform, had no clinically relevant effect on exposure to pomalidomide relative to that exposure to pomalidomide observed in non-smokers.

Dexamethasone: Co-administration of multiple doses of 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak inducer of CYP3A) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.

15.27 **Known potential toxicities**:

**Very common known potential toxicities, ≥10%**:
Anemia, leukopenia, neutropenia, thrombocytopenia, constipation, diarrhea, nausea, fatigue, peripheral edema, pyrexia, bronchitis, pneumonia, upper respiratory tract infection, decreased appetite, bone pain, muscle spasm, dizziness, peripheral neuropathy, blood creatinine increased, acute renal failure, cough, dyspnea, pruritis

**Common known potential toxicities, ≥1% - <10%**:
Febrile neutropenia, pancytopenia, vertigo, vomiting, gastrointestinal hemorrhage, hemorrhoidal hemorrhage, rectal hemorrhage, hematochezia, gingival bleeding, bronchopneumonia, herpes zoster, nasopharyngitis, neutropenic sepsis, respiratory tract infection, alanine aminotransferase increased, increased liver function test, aspartate aminotransferase increased, gamma-glutamyltransferase increased, neutrophil count decreased, platelet count decreased, white blood cell count decreased, hyperkalemia, hyponatremia, depressed level of consciousness, peripheral sensory neuropathy, paresthesia, gait disturbance, polyneuropathy, hypoesthesia, neuralgia, peripheral motor neuropathy, tremor, confusional state, renal failure, renal impairment, hypercreatininemia, urinary retention, pelvic pain, pulmonary embolism, pruritus generalized, rash, swelling face, face edema, deep vein thrombosis

**Uncommon and rare known potential toxicities, <1%**:
Melena, Mallory-Weiss syndrome, upper gastrointestinal hemorrhage, mucosal hemorrhage, hyperbilirubinemia, blood bilirubin increased, transaminases increased, blood alkaline phosphates increased, liver function test abnormal, basil cell carcinoma, dysethesia, areflexia, motor dysfunction, sensory disturbance, burning sensation, muscle atrophy, blood urea increased, creatinine renal clearance decreased, oliguria, glomerular filtration rate decreased, renal tubular necrosis, acute prerenal failure, azotemia, pneumonitis, interstitial lung disease, pruritis generalized, angioedema, urticarial, eyelid edema

**Frequency not defined:**

Hepatitis, hepatitis B viral reactivation, tumor lysis syndrome, squamous cell carcinoma of skin, eye swelling, periorbital edema, lip swelling, swollen tongue, mouth edema, pharyngeal edema, Stevens-Johnson syndrome, toxic epidermal necrolysis, drug reaction with eosinophilia and systemic symptoms (DRESS)

All study participants must be registered into the mandatory POMALYST REMS™ program, and be willing and able to comply with the requirements of the POMALYST REMS™ program. Females of reproductive potential must adhere to the scheduled pregnancy testing. Females of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves.

15.28 **Drug procurement:** Pomalidomide (POMALYST®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with Celgene Corporation's POMALYST REMS™ program. Per the standard POMALYST REMS™ program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle.

15.3 Dexamethasone for Oral Administration (DXM)

15.31 **Background**: Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

15.32 **Formulation**: Commercially available for oral administration as:
Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg
Solution, oral: 0.5 mg/mL (500 mL)
Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL)

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (60ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use

if solution contains a precipitate. Refer to commercial package for drug expiration date.

15.34 **Administration:** Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.

15.35 **Pharmacokinetic information**:

**Onset of action:** Prompt

**Duration of metabolic effect:** 72 hours

**Metabolism:** Hepatic

**Half-life elimination:** Normal renal function: 1.8-3.5 hours; **Biological half-life:** 36-54 hours

**Time to peak, serum:** Oral: 1-2 hours

**Excretion**: Urine and feces

15.36 **Potential Drug Interactions**:

**Cytochrome P450 Effect: Substrate** of CYP3A4 (major); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong)
**Increased Effect/Toxicity:** Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.
**Decreased Effect:** Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
**Ethanol/Nutrition/Herb Interactions**:
Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
Herb/Nutraceutical: Avoid cat's claw (*Uncaria tomentosa)*, echinacea (have immunostimulant properties)

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.

**Common known potential toxicities,** frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, 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 hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

## 16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase II study of a novel regimen of ixazomib with pomalidomide and dexamethasone for treatment of multiple myeloma with extramedullary disease and plasma cell leukemia. The study is designed to assess the confirmed response rate using a single stage phase II study design with an interim analysis. Accrual will be halted after 6 patients to assess safety (see Section 16.4). We do not plan to halt accrual during the interim analysis (see Section 16.214).

16.11 Primary Endpoint: The primary endpoint of this trial is the rate of confirmed response. A confirmed response is defined as a patient who has achieved an sCR, CR, VGPR, or PR on two consecutive evaluations. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment, will be evaluable for response, unless they are determined to be a major violation.

16.2 Statistical Design

16.21 Decision Rule: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 25%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 50%. The following one–stage design with an interim analysis is based on a two-stage Simon optimum design and requires 27 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 25%.

16.211 Interim Analysis: Enter 10 evaluable patients into the study. If 2 or fewer successes are observed in the first 10 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if the number of successes is at least 3, we will continue accrual.

16.212 Final Decision Rule: Enter an additional 17 evaluable patients into the study. If 9 or fewer successes are observed in the first 27 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 10, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies in this population.

16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.313.

16.214 NOTE: We will not suspend accrual at the interim analysis to allow the first 10 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.22 Sample Size: The one stage study design with an interim analysis to be used is fully described below. A minimum of 10 and a maximum of 27 evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. We anticipate accruing additional 3 patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a total of 30 patients overall.

16.23 Accrual Rate and Study Duration: The anticipated accrual rate is 1-2 evaluable multiple myeloma patients per month. At this rate, it will likely take about 18-24 months to enroll, treat, and evaluate all patients. The maximum total study duration is expected to be approximately 2.5 years, or until the last patient accrued has been observed for at least 6 months.

16.24 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e. there is a 10% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping at the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

| If the true success proportion is... | 0.25 | 0.30 | 0.35 | 0.40 | 0.45 | 0.50 |
|---|---|---|---|---|---|---|
| Then the probability of declaring that the regimen warrants further study is… | 0.10 | 0.24 | 0.44 | 0.64 | 0.80 | 0.90 |
| And the probability of stopping at the interim analysis is… | 0.53 | 0.38 | 0.26 | 0.17 | 0.10 | 0.05 |

16.25 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study.

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

16.31 Primary Outcome Analyses:

16.311 Definition: The primary endpoint of this trial is the proportion of the confirmed response rate. A success is defined as an sCR, CR, VGPR, or PR noted as the objective status on two consecutive evaluations. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Ninety-

five percent confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.

16.313 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.32 Secondary Outcome Analyses

16.321 Type of response will be differentiated as biochemical vs. extramedullary disease, as defined in Section 11.6. Biochemical response will be defined as a response by serum M-protein, urine M-protein, or serum FLC assay parameters. For biochemical response, the response rate will be estimated by the number of responders divided by the number of evaluable patients who have measurable disease by serum M-protein, urine M-protein, or serum FLC assay at baseline. Extramedullary response will be defined as a response by extramedullary plasmacytoma or plasma cell count parameters. For extradmedullary response, the response rate will be estimated by the number of responders divided by the number of evaluable patients. Exact binomial confidence intervals will be calculated.

16.322 Progression-free survival is defined as the time from registration to the earliest date of documentation of disease progression or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.

16.323 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the study treatment will be taken into consideration.

16.33 Correlative Analyses

16.331 Minimal residual disease will be assessed on bone marrow aspirate in all patients achieving CR. The proportion of patients who achieve MRD negative status will be estimated by the number of patients who are MRD negative divided by the total number of evaluable patients who achieve an sCR or CR. Exact binomial 95% confidence intervals for the true MRD negative rate will be calculated.

16.4 Early Safety Analysis

An early safety analysis will be performed after the first 6 patients have been accrued to the study and observed for one cycle. Accrual will be temporarily halted while these patients are evaluated. If 2 or more of the first 6 patients experience a DLT as defined below, then accrual to the study will continue to be temporarily halted while the study team determines if changes to the dosing schedule are warranted.

Toxicity will be measured per NCI-CTCAE version 4. DLT is defined as an adverse event occurring during the first cycle of treatment that is possibly, probably, or definitely related to study treatment and that meets one of the following:

- Grade 3 diarrhea, nausea, and fatigue lasting > 3 days despite optimal supportive medications
- Any other ≥Grade 3 non-hematological toxicity with the exceptions of electrolyte abnormalities that are reversible and asymptomatic
- Febrile neutropenia
- Grade 3 thrombocytopenia with clinically significant bleeding
- Any ≥Grade 4 neutrophil count decreased or platelet count decreased that persists >7 days

16.5 Data & Safety Monitoring:

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible,” “probable,” or “definite”) that satisfy one of the following:

- if 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 15 patients have been treated, 30% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.6 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the “ClincialTrails.gov” website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2.5 years after the study opens to accrual. The definition of “Primary Endpoint Completion Date” (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.7 Inclusion of Women and Minorities

16.71 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.

16.72 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.73 The geographical region served by MCCC has a population which includes approximately 3% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

**Accrual Estimates by Gender/Ethnicity/Race**

| Ethnic Category | Sex/Gender | | | |
|---|---|---|---|---|
| | **Females** | **Males** | **Unknown** | **Total** |
| Hispanic or Latino | 0 | 1 | 0 | 1 |
| Not Hispanic or Latino | 10 | 19 | 0 | 29 |
| **Ethnic Category: Total of all subjects*** | 10 | 20 | 0 | **30** |
| **Racial Category** | | | | |
| American Indian or Alaskan Native | 0 | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 | 0 |
| Black or African American | 1 | 1 | 0 | 2 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 | 0 |
| White | 9 | 19 | 0 | 28 |
| **Racial Category: Total of all subjects*** | 10 | 20 | 0 | **30** |

**Ethnic Categories:**

**Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

**Racial Categories:**

**American Indian or Alaskan Native –** a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

**Asian –** a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

**Black or African American –** a person having origins in any of the black racial groups of Africa. Terms such as "Haitian" or "Negro" can be used in addition to "Black or African American."

**Native Hawaiian or other Pacific Islander –** a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

**White –** a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

## 17.0 Pathology Considerations/Tissue Biospecimens

None

## 18.0 Records and Data Collection Procedures

18.1 Submission Timetable
Data submission instructions for this study can be found in the Case Report Form packet.

18.2 Event monitoring
See Section 4.2 for the event monitoring schedule.

18.3 CRF completion for non-Mayo Clinic sites
This study will use Medidata Rave for remote data capture (rdc) of all study data.

18.4 Site responsibilities
Each co-sponsor/participant will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation
This study requires supporting documentation for diagnosis and progression prior to study entry as well as for evidence of response to study therapy and progression after study therapy. Supporting documentation for diagnosis will include either a pathology report or a laboratory report demonstrating multiple myeloma with extramedullary disease or plasma cell leukemia (including bone marrow biopsy report; and SPEP, UPEP, FLC, FISH, and Cytogenetics reports). These reports should be submitted within 14 days of registration.

For progression of disease prior to study entry, supporting documentation includes the evidence needed to determine the patient's progression prior to enrollment. These documents should be submitted within 14 days of registration.

For response to treatment, supporting documentation includes SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, and X-ray skeletal survey.

For patients who progress after study therapy supporting documentation may include any of the following: SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, and X-ray skeletal survey.

18.6 Labelling of materials
Each site will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Incomplete materials
Any data entered into a form will result in that form being marked as "received." However, missing data will be flagged by edit checks in the database.

18.8 Overdue lists
The list of overdue materials is available in the database at any time. A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration

number. The appropriate co-sponsor/participant will be responsible to obtain the overdue material.

18.9 Corrections forms
If a correction is necessary the QAS will query the site. The query will be sent to the appropriate site to make the correction in the database and respond back to the QAS.

## 19.0 Budget

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: None

19.3 Other budget concerns: None

## 20.0 References

Gupta, N., M. Saleh and K. Venkatakrishnan (2011). "Flat-dosing versus BSA-based dosing for MLN9708, an investigational proteasome inhibitor: population pharmacokinetic (PK) analysis of pooled data from 4 phase-1 studies. ." Blood **118**(21): 1433.

Gupta, N., M. Saleh and K. Venkatakrishnan (2012). "Switch from BSA-based dosing to fixed dosing for the investigational drug ixazomib citrate: Application of modeling and simulation to influence posology decisions in oncology drug development. ." Clin Pharmacol Ther **91**(S86-S87 ).

Kumar, S., S. V. Rajkumar, R. A. Kyle, M. Q. Lacy, A. Dispenzieri, R. Fonseca, J. A. Lust, M. A. Gertz, P. R. Greipp and T. E. Witzig (2005). "Prognostic value of circulating plasma cells in monoclonal gammopathy of undetermined significance." J Clin Oncol **23**(24): 5668-5674.

Kumar, S. K., W. I. Bensinger, T. M. Zimmerman, C. B. Reeder, J. R. Berenson, D. Berg, A. M. Hui, N. Gupta, A. Di Bacco, J. Yu, Y. Shou and R. Niesvizky (2014). "Phase 1 study of weekly dosing with the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma." Blood **124**(7): 1047-1055.

Kumar, S. K., W. I. Bensinger, T. M. Zimmerman, C. B. Reeder, J. R. Berenson, D. Berg, A. M. Hui, N. Gupta, A. Di Bacco, J. Yu, Y. Shou and R. Niesvizky (2014). "Weekly dosing of the investigational oral proteasome inhibitor ixazomib in relapsed/refractory multiple myeloma: results from a phase 1 study." Blood.

Kumar, S. K., J. G. Berdeja, R. Niesvizky, S. Lonial, J. P. Laubach, M. Hamadani, A. K. Stewart, P. Hari, V. Roy, R. Vescio, J. L. Kaufman, D. Berg, E. Liao, A. Di Bacco, J. Estevam, N. Gupta, A. M. Hui, V. Rajkumar and P. G. Richardson (2014). "Safety and tolerability of ixazomib, an oral proteasome inhibitor, in combination with lenalidomide and dexamethasone in patients with previously untreated multiple myeloma: an open-label phase 1/2 study." Lancet Oncol **15**(13): 1503-1512.

Lacy, M. Q., J. B. Allred, M. A. Gertz, S. R. Hayman, K. D. Short, F. Buadi, A. Dispenzieri, S. Kumar, P. R. Greipp, J. A. Lust, S. J. Russell, D. Dingli, S. Zeldenrust, R. Fonseca, P. L. Bergsagel, V. Roy, A. K. Stewart, K. Laumann, S. J. Mandrekar, C. Reeder, S. V. Rajkumar and J. R. Mikhael (2011). "Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: comparison of 2 dosing strategies in dual-refractory disease." Blood **118**(11): 2970-2975.

Lacy, M. Q., S. R. Hayman, M. A. Gertz, A. Dispenzieri, F. Buadi, S. Kumar, P. R. Greipp, J. A. Lust, S. J. Russell, D. Dingli, R. A. Kyle, R. Fonseca, P. L. Bergsagel, V. Roy, J. R. Mikhael, A. K. Stewart, K. Laumann, J. B. Allred, S. J. Mandrekar and S. V. Rajkumar (2009). "Pomalidomide (CC4047) plus low-dose dexamethasone as therapy for relapsed multiple myeloma." J Clin Oncol **27**(30): 5008-5014.

Lacy, M. Q., S. R. Hayman, M. A. Gertz, K. D. Short, A. Dispenzieri, S. Kumar, P. R. Greipp, J. A. Lust, S. J. Russell, D. Dingli, S. Zeldenrust, R. Fonseca, P. L. Bergsagel, V. Roy, J. R. Mikhael, A. K. Stewart, K. Laumann, J. B. Allred, S. J. Mandrekar, S. V. Rajkumar and F. Buadi (2010). "Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM)." Leukemia **24**(11): 1934-1939.

Leleu, X., L. Karlin, M. Macro, C. Hulin, L. Garderet, M. Roussel, B. Arnulf, B. Pegourie, B. Kolb, A. M. Stoppa, S. Brechiniac, G. Marit, B. Thielemans, B. Onraed, C. Mathiot, A. Banos, L. Lacotte, M. Tiab, M. Dib, J. G. Fuzibet, M. O. Petillon, P. Rodon, M. Wetterwald, B. Royer, L. Legros, L. Benboubker, O. Decaux, M. Escoffre-Barbe, D. Caillot, J. P. Fermand, P. Moreau, M. Attal, H. Avet-

Loiseau and T. Facon (2015). "Pomalidomide plus low-dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4;14): IFM 2010-02." Blood.

Lopez-Anglada, L., N. C. Gutierrez, J. L. Garcia, M. V. Mateos, T. Flores and J. F. San Miguel (2010). "P53 deletion may drive the clinical evolution and treatment response in multiple myeloma." Eur J Haematol **84**(4): 359-361.

Madan, S. and S. Kumar (2009). "Review: extramedullary disease in multiple myeloma." Clin Adv Hematol Oncol **7**(12): 802-804.

Richardson, P. G., R. Baz, M. Wang, A. J. Jakubowiak, J. P. Laubach, R. D. Harvey, M. Talpaz, D. Berg, G. Liu, J. Yu, N. Gupta, A. Di Bacco, A. M. Hui and S. Lonial (2014). "Phase 1 study of twice-weekly dosing of investigational oral proteasome inhibitor ixazomib in patients with relapsed and/or refractory multiple myeloma." Blood.

Rosinol, L., M. T. Cibeira, J. Blade, J. Esteve, M. Aymerich, M. Rozman, M. Segarra, M. C. Cid, X. Filella and E. Montserrat (2004). "Extramedullary multiple myeloma escapes the effect of thalidomide." Haematologica **89**(7): 832-836.

San Miguel, J., K. Weisel, P. Moreau, M. Lacy, K. Song, M. Delforge, L. Karlin, H. Goldschmidt, A. Banos, A. Oriol, A. Alegre, C. Chen, M. Cavo, L. Garderet, V. Ivanova, J. Martinez-Lopez, A. Belch, A. Palumbo, S. Schey, P. Sonneveld, X. Yu, L. Sternas, C. Jacques, M. Zaki and M. Dimopoulos (2013). "Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial." Lancet Oncol **14**(11): 1055-1066.

Sheth, N., J. Yeung and H. Chang (2009). "p53 nuclear accumulation is associated with extramedullary progression of multiple myeloma." Leuk Res **33**(10): 1357-1360.

Short, K. D., S. V. Rajkumar, D. Larson, F. Buadi, S. Hayman, A. Dispenzieri, M. Gertz, S. Kumar, J. Mikhael, V. Roy, R. A. Kyle and M. Q. Lacy (2011). "Incidence of extramedullary disease in patients with multiple myeloma in the era of novel therapy, and the activity of pomalidomide on extramedullary myeloma." Leukemia **25**(6): 906-908.

Streetly, M. J., K. Gyertson, Y. Daniel, J. B. Zeldis, M. Kazmi and S. A. Schey (2008). "Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation." British journal of haematology **141**(1): 41-51.

Usmani, S. Z., C. Heuck, A. Mitchell, J. Szymonifka, B. Nair, A. Hoering, Y. Alsayed, S. Waheed, S. Haider, A. Restrepo, F. Van Rhee, J. Crowley and B. Barlogie (2012). "Extramedullary disease portends poor prognosis in multiple myeloma and is over-represented in high-risk disease even in the era of novel agents." Haematologica **97**(11): 1761-1767.

Varettoni, M., A. Corso, G. Pica, S. Mangiacavalli, C. Pascutto and M. Lazzarino (2009). "Incidence, presenting features and outcome of extramedullary disease in multiple myeloma: a longitudinal study on 1003 consecutive patients." Ann Oncol **21**(2): 325-330.

## Appendix I ECOG Performance Status

| ECOG PERFORMANCE STATUS* | |
|---|---|
| **Grade** | **ECOG** |
| 0 | Fully active, able to carry on all pre-disease performance without restriction |
| 1 | Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work |
| 2 | Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours |
| 3 | Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours. |
| 4 | Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair. |
| 5 | Dead |

*As published in Am. J. Clin. Oncol.:
*Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.*

The ECOG Performance Status is in the public domain therefore available for public use. To duplicate the scale, please cite the reference above and credit the Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

From [redacted]

## Appendix II Patient Medication Diary

**Name**_____ __ **Study ID Number**_____

Please complete this diary on a daily basis. Write in the amount of the dose of pomalidomide, ixazomib, and dexamethasone that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". If you forget to take your daily dose, please write in "0", but remember to take your prescribed dose at the next regularly scheduled time.

Please drink at least 6 to 8 cups of liquid per day to help drug absorption. Swallow pills whole, with water, and do not to break, chew, crush or open the pills. 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 pill should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the pills.

If you experience any health/medical complaints or take any medication other than pomalidomide, ixazomib, or dexamethasone, please record this information.

Week of: _____

| ***Study Drug*** | ***Day 1*** | ***Day 2*** | ***Day 3*** | ***Day 4*** | ***Day 5*** | ***Day 6*** | ***Day 7*** |
|---|---|---|---|---|---|---|---|
| Pomalidomide | | | | | | | |
| Ixazomib | | | | | | | |
| Dexamethasone | | | | | | | |

Week of: _____

| ***Study Drug*** | ***Day 8*** | ***Day 9*** | ***Day 10*** | ***Day 11*** | ***Day 12*** | ***Day 13*** | ***Day 14*** |
|---|---|---|---|---|---|---|---|
| Pomalidomide | | | | | | | |
| Ixazomib | | | | | | | |
| Dexamethasone | | | | | | | |

Week of: _____

| ***Study Drug*** | ***Day 15*** | ***Day 16*** | ***Day 17*** | ***Day 18*** | ***Day 19*** | ***Day 20*** | ***Day 21*** |
|---|---|---|---|---|---|---|---|
| Pomalidomide | | | | | | | |
| Ixazomib | | | | | | | |
| Dexamethasone | | | | | | | |

Week of: _____

| ***Study Drug*** | ***Day 22*** | ***Day 23*** | ***Day 24*** | ***Day 25*** | ***Day 26*** | ***Day 27*** | ***Day 28*** |
|---|---|---|---|---|---|---|---|
| Pomalidomide | | | | | | | |
| Ixazomib | | | | | | | |
| Dexamethasone | | | | | | | |

Patient Signature: _____

**My next scheduled visit is:** _____

If you have any questions, please call: _____

Bring *all* bottles and any unused study medication along with this diary when you return for your next appointment.

**Study Coordinator Use Only**

Number of pills returned Number of vials returned:

Discrepancy Yes____/No____ Verified by _____ Date_____

## Appendix III Drug Classification Guide

| Class | Generic name | Other Names | |
|---|---|---|---|
| **Alkylators** | | | |
| | Cyclophosphamide | Cytoxan | |
| | Melphalan | Alkeran | |
| | Carmustine | BCNU | |
| | Busulphan | Myleran | |
| | Chlorambucil | | |
| | Cisplatin | | |
| | Dacarbazine | | |
| | Ifosfamide | | |
| | Lomustine | CCNU | |
| | Mecholorethamine | Nitrogen mustard | |
| | Procarbazine | | |
| **Antimetabolites** | | | |
| | Asparaginase | | |
| | Chlorodeoxyadenosine | 2-CDA | |
| | Cytabarine | Cytosar-U | Tarabine |
| | Deoxycorormycin | | |
| | Floxuridine | | |
| | Fludarabine | | |
| | Flurouracil | | |
| | Hydroxyurea | | |
| | Mercaptopurine | | |
| | Methotrexate | | |
| | Thioguanine | | |
| | Thiotepa | | |
| **Anthracyclines/Antibiotics** | | | |
| | Bleomycin | | |
| | Dactinomycin | | |
| | Daunorubicin | | |
| | Doxorubicin | Adriamycin | |
| | Pegylated doxorubicin | Doxyl | |
| | Idarubicin | | |
| | Mitomycin | | |
| | Mitoxantrone | | |
| **Bisphosphonates** | | | |
| | Zoledronic acid | Zometa | |
| | Pamidronate | Aredia | |
| **Corticosteroids** | | | |
| | Prednisone | | |

| | | |
|---|---|---|
| Methylprednisolone | Solumedrol | |
| Dexamthasone | Decadron | Dex |

**IMiDs (immune modulatory drugs)**

| | | |
|---|---|---|
| Thalidomide | Thalidomid | |
| Lenalidomide | Revlimid | CC-5013 |
| Interferon | | |
| Pomalidomide | | |
| Levamisole | | |

**Proteasome inhibitors**

| | |
|---|---|
| Bortezomib | Velcade |
| Carfilzomib | Kyprolis |
| MLN9708 | Ixazomib |
| Oprozomib | |

**Topoisomerases**

| | |
|---|---|
| Etoposide | VP-16 |

**Taxanes**

| | |
|---|---|
| Paclitaxel | Taxol |
| Docetaxel | |

**Monoclonal Antibodies**

| | |
|---|---|
| Anti-SLAMF7 | Elotuzumab |
| Anti-38 | Daratumumab |

**Vinca Alkyloid**

Vinblastine
Vincristine
Vindestine
Vinorelbine

**Last Updated 9/29/14**

## Appendix IV Pomalidomide Education and Counselling Guidance Document

**NOTE: This document will be completed as part of the Pomalyst REMS program. It is included here for informational purposes only.**

Protocol Number: MC1487_____

Patient Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

**(Check the appropriate box to indicate risk category)**

Female:___

If female, check one:

___FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

___NOT FCBP

Male:_____

**Do Not Dispense study drug if:**

- **The patient is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].**

**FCBP:**

1. I verified that the required pregnancy tests performed are negative.
2. I counselled FCBP regarding the following:
    - Potential risk of fetal exposure to pomalidomide: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.
    - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
    - That even if she has amenorrhea she must comply with advice on contraception.

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the patient.

**FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):**

1. I counselled the female NOT of childbearing potential regarding the following:
    - Potential risk of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
    - NEVER share study drug with anyone else.
    - Do not donate blood while taking study drug and for 28 days after stopping study drug.
    - Do not break, chew, or open study drug capsules
    - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the patient.

**MALE:**

1. I counselled the Male patient regarding the following:
    - Potential study drug fetal exposure to pomalidomide (Refer to item #2 in FCBP).
    - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
    - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant
    - NEVER share study drug with anyone else.
    - Do not donate blood while taking study drug and for 28 days after stopping study drug.
    - Do not donate semen or sperm while taking study drug and for 28 days after stopping study drug.
    - Do not break, chew, or open study drug capsules.
    - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the patient.

Investigator/Counselor Name (Print): _____
(circle applicable)

Investigator/Counselor Signature: _____ Date: _____/_____/_____
(circle applicable)

**Maintain a copy of the Education and Counselling Guidance Document in the patient records.**

**Pomalidomide Information Sheet**

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

***What is the most important information I should know about pomalidomide?***

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits. **If you are a female who is able to become pregnant:**

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting study drug
     - while taking study drug
     - during dose interruptions of study drug
     - for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**
     - within 10 – 14 days and again 24 hours prior to the first dose of study drug
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking study drug if you become pregnant during treatment**
     - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking study drug**
   - The study doctor will be able to advise you where to get additional advice on contraception.

   **If you are a female not of childbearing potential:**

   In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

   **If you are a male:**

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to the foetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

1. Male patients (including those who have had a vasectomy) must either **not have any sexual relations with a pregnant female or a female who can become pregnant,** or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
    - While you are taking study drug
    - During dose interruptions of study drug
    - For 28 days after you stop taking study drug
2. **Male patients should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
3. **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

**2. Restrictions in sharing study drug and donating blood:**

1. **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
2. **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
3. **Do not break, chew, or open study drug capsules.**
4. You will be supplied with no more than one cycle of study drug
5. Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

## Appendix V MC1487 Model Consent Form

***NOTES FOR LOCAL INVESTIGATORS:**

*The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The website address for this document is* http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/

- *A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.*
- *Instructions and examples for informed consent authors are in [italics]. Remember to remove these items before finalizing your consent form.*
- *The language should be written in 6th grade language. When proofreading the consent form, ask yourself if an average 6th grader would understand the study after reading this form.*
- *Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials." This pamphlet may be ordered on the NCI website at https://cissecure.nci.nih.gov/ncipubs/ or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.*
- *Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.*

**These notes for investigators are instructional and should not be included in the informed consent form given to the prospective research participant.*

---

# RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

**Study Title:** MC1487: Phase 2 Trial of Pomalidomide, Ixazomib and Dexamethasone in Patients with Multiple Myeloma with Extramedullary Disease or Plasma Cell Leukemia {MMRC-052}

**IRB#:** *{Insert local IRB number here}*

**Principal Investigator:** *{Insert name of local investigator here}*

Please read this information carefully. It tells you important things about this research study. A member of our research team will talk to you about taking part in this research study. If you have questions at any time, please ask us.

Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you make your decision.

To help you decide if you want to take part in this study, you should know:

- Taking part in this study is completely voluntary.
- You can choose not to participate.
- You are free to change your mind at any time if you choose to participate.
- Your decision won't cause any penalties or loss of benefits to which you're otherwise entitled.
- Your decision won't change the access to medical care you receive now or in the future if you choose not to participate or discontinue your participation.

For purposes of this form, Mayo Clinic refers to Mayo Clinic in Arizona, Florida and Rochester, Minnesota; Mayo Clinic Health System; and all owned and affiliated clinics, hospitals, and entities.

If you decide to take part in this research study, you will sign this consent form to show that you want to take part. We will give you a copy of this form to keep. A copy of this form will be put in your medical record.

## CONTACT INFORMATION

| You can contact … | At … | If you have questions or about … |
|---|---|---|
| **Principal Investigator:**<br>*Insert local PI Name*<br><br>**Study Team Contact:**<br>*Insert local contact here* | **Phone:**<br>*Insert local telephone*<br><br>**Phone:**<br>*Insert local telephone*<br><br>**Address:**<br>*Insert local address* | ▪ Study tests and procedures<br>▪ Research-related injuries or emergencies<br>▪ Any research-related concerns or complaints<br>▪ Withdrawing from the research study<br>▪ Materials you receive<br>▪ Research-related appointments |
| **Institutional Review Board (IRB)/Research Ethics Board (REB)** | **Phone:**<br>*Insert IRB/REB telephone*<br><br>**Toll-Free:** | ▪ Rights of a research participant |
| **Research Subject Advocate**<br>**(The RSA is independent of the Study Team)** | **Phone:**<br>*Insert local telephone*<br><br>**E-mail:** | ▪ Rights of a research participant<br>▪ Any research-related concerns or complaints<br>▪ Use of your Protected Health Information<br>▪ Stopping your authorization to use your Protected Health Information |

| You can contact … | At … | If you have questions or about … |
|---|---|---|
| **Research Billing** | *Insert local telephone* | ▪ Billing or insurance related to this research study |

**Other Information:**

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

## 1. Why are you being asked to take part in this research study?

You are being asked to take part in this study because you have been diagnosed with a type of blood cancer called "multiple myeloma" that requires treatment.

About 30 people will take part in this research study.

## 2. Why is this research study being done?

You are being asked to take part in this research study because your multiple myeloma has gotten worse and is not responding to the standard drugs for multiple myeloma.

In this study, you will be treated with an investigational drug called ixazomib (MLN9708), in addition to the standard regimen of pomalidomide and dexamethasone. It is thought that ixazomib will interfere with the process of protein breakdown in the multiple myeloma cells. The drug used in this study is considered investigational, which means it has either not been approved by the Food and Drug Administration (FDA) for routine clinical use or for the use described in this study. This study is being done to find out what effects (good and bad) the ixazomib has on you and your Multiple Myeloma.

## 3. Information you should know

**Who is Funding the Study?**

Takeda Pharmaceuticals/Millennium Pharmaceuticals, Celgene Corporation, and the Multiple Myeloma Research Foundation/Consortium (MMRF/MMRC) are funding the study. MMRF/MMRC will pay Mayo Clinic and other study sites to cover costs related to running the study.

**Information Regarding Conflict of Interest:**

Your doctor may be referring you to this study and if your doctor is also an Investigator in this study, he or she has a conflict by having two sets of interests (your well-being, and the scientific conduct of the study). If you are uncomfortable with your doctor working with you as part of this research study, but still wish to participate in the research, you may request to work with a different member of the research team.

## 4. How long will you be in this research study?

You will be in the study for approximately 3 years.

## 5. What will happen to you while you are in this research study?

**Before you begin the study:**

If you agree to be in the study, you first sign this Informed Consent form, then you will be asked to participate in the following:

**Prior to Registration**

- Physical exam including complete medical history, height, weight and vital signs (blood pressure, heart rate, pulse, etc.)
- Routine blood and urine tests
- Skeletal survey (X-ray or low dose whole body CT) if needed
- CT, MRI or CT-PET scan
- Chest x-ray
- Pregnancy test
- Bone marrow aspirate and biopsy
- ECG (a test to see how your heart is working)
- Research blood tests
- ECOG performance status (assessment of your ability to carry out daily activities)
- Research samples (bone marrow and blood)

As part of your clinical care, you will automatically be enrolled in the Pomalyst® REMS program in order to obtain pomalidomide. Before you can be enrolled in this program, you must read and agree to all the instructions. Due to the risks of the drug, pomalidomide is only

available through this program. More information is available on this website: http://www.pomalystrems.com/patient.html.

**Every Cycle Pre-treatment**

- Routine blood and urine tests
- Physical exam including complete medical history, height, weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- CT, MRI or CT-PET scan (at the end of Cycle 1, then every third cycle)
- Medication diary (please bring your medication diary with you to each visit)

If you are a female of childbearing potential, you will need to have a blood or urine pregnancy test done weekly for the first four weeks of the study and every 28 days while on therapy with pomalidomide and/or ixazomib. In addition, you will need a pregnancy testing until 90 days after your last dose of ixazomib.

**Day 8, 15, 22 (Cycles 1-3); Day 15 (Cycle 4 onwards)**

- Routine blood tests

**End of Cycle 4 and every fourth cycle**

- Bone marrow aspirate and biopsy
- Research samples (bone marrow and blood)

**End of Treatment**

- Physical exam including complete medical history, height, weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood and urine tests
- Skeletal survey (x-ray or CT) if needed
- Medication diary
- Bone marrow aspirate and biopsy
- Research samples (bone marrow and blood)

## 6. What are the possible risks or discomforts from being in this research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. In some cases, side effects can be serious, long lasting, or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

## POTENTIAL DISCOMFORTS AND RISKS OF IXAZOMIB

Based on early studies of ixazomib, it is possible to predict some of the discomforts and risks. The data suggest that the potential risks of ixazomib are likely to be manageable if monitored and treated. However, risks could become serious and potentially life-threatening. It is possible that ixazomib may cause side effects that were not seen in animal studies or yet seen in patients.

**Common risks of ixazomib** (events occurring greater than 20% of the time)

- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Loose stools (diarrhea)
- Constipation
- Feeling tired or weak
- Decreased number of blood cells (platelets) that help to clot the blood, which could put you at increased risk of bleeding (thrombocytopenia)
- Swelling of extremities
- Fever
- Decrease in red blood cells, which are the oxygen carrying cells which could make you feel tired (anemia)
- A low number of white blood cells, which are the infection fighting cells, which could put you at risk for infection (neutropenia)
- Infection including shingles
- Skin rash
- A low number of a particular white blood cell, which is important to the immune system (lymphopenia)
- Numbness and tingling (also known as peripheral neuropathy)

**Less likely risks of ixazomib** (events occurring less than or equal to 20% of the time)

- Decreased appetite (not feeling hungry, not wanting to eat)
- Cough
- Joint pain
- Abdominal pain or distension
- Difficulty sleeping
- Back pain
- Shortness of breath
- Upper respiratory tract infection
- Sensation of lightheadedness or vertigo (spinning sensation) (dizziness)
- Blood chemical imbalance (electrolyte imbalance)
- Headache
- Excessive or abnormal loss of body fluids (dehydration)
- Pneumonia

**Rare risks of ixazomib** (events occurring less than 2-3% of the time)

- Low or high blood pressure
- A painful blistery red rash that is confined to one side of the body, similar to chicken pox (shingles - herpes zoster)
- Effects on your nervous system that may cause painful feelings or numbness or tingling in hands and feet. The nerves that control things like your heart rate, gut movement, and urinary bladder may be affected.
- Inflammatory response associated with an increase in your white blood cell count, fever, and a change in certain protein levels and chemistries in the body
- Esophageal ulcer
- Chest pain
- Abnormal liver tests
- Decreased weight
- Fainting episodes
- Decreased level of consciousness
- Tremors
- Blood clots
- Inflammation of the lungs
- Increased blood pressure in the lungs
- Nosebleeds
- Muscle weakness
- Changes in mood
- Swelling around the eyes
- Muscle aches

**Rare but serious risks of ixazomib**

- Life threatening severe skin rash
- Abnormal heart rhythms
- Worsening of your heart function (congestive heart failure)
- Disorders of your lungs that could be serious enough to result in death
- Liver failure
- Abnormal clotting of the blood in small blood vessels (Thrombotic Thrombocytopenic Purpura [TTP[)
- A complication that may occur if the cancer cells die too quickly that includes inappropriate increase or decrease of various natural chemicals in the blood stream, called uric acid, phosphorus, potassium, creatinine, and calcium. Severe tumor lysis can result in kidney failure and may harm muscle or nerve function (Tumor lysis syndrome)
- High creatinine and renal failure. The amount of creatinine (a waste product made by your body) in your blood helps your doctor understand how your kidneys are working. High creatinine means your kidneys are having trouble working well. Patients who had lost body water 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).
- Blockage of your bowel function

- Severe rash that can lead to skin peeling and life-threatening complications (Stevens Johnson syndrome)
- A condition that can be linked to abnormal nerve function and seizures (posterior reversible encephalopathy syndrome [PRES])
- Inflammation of the spinal cord (transverse myelitis)

Progressive multifocal leukoencephalopathy (PML) has been reported with ixazomib in an oncology patient who had previously received a medication associated with PML. 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. It is not known whether ixazomib may have contributed to the development PML in this patient.

Ixazomib should not be taken if you have ever had a serious allergic reaction to boron or boron containing products.

**POTENTIAL DISCOMFORTS AND RISKS OF POMALIDOMIDE (CC-4047, Pomalyst®)**

**Likely risks of pomalidomide** *(events occurring greater than 20% of the time)*

- A low number of white blood cells, which are the infection fighting cells, which could put you at risk for infection (neutropenia or leukopenia)
- A low number of a particular white blood cell, which is important to the immune system (lymphopenia)
- Feeling tired (fatigue)
- Difficulty passing stool (constipation)
- Feeling sick to your stomach (nausea)
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding (thrombocytopenia)
- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (anemia)
- Back pain
- Shortness of breath or difficulty breathing (dyspnea)
- Loose stools (diarrhea)
- Bronchitis
- Upper respiratory tract infection
- Pneumonia
- Dizziness
- Nerve damage (peripheral neuropathy)
- Decreased appetite
- Swelling of limbs (peripheral edema)
- Fever
- Bone pain
- Muscle spasm
- Cough
- Kidney failure (renal failure)

- Nausea
- Generalized weakness (asthenia)

**Less likely risks of pomalidomide** *(events occurring less than or equal to 20% of the time)*

- When pomalidomide or related drugs (i.e. thalidomide and lenalidomide) have been used along with corticosteroids and certain other chemotherapy drugs, there has been an increased risk of individuals developing blood clots including blood clots in the big veins of the limbs (deep vein thrombosis) or in the lungs (pulmonary embolism). Your doctor may request or require that you take aspirin or another blood thinner in this situation.
- Abdominal pain
- Sore mouth, nose, or throat (nasopharyngitis)
- Drop in blood pressure
- Headache
- Chest pain
- Feeling shaky (tremor)
- 
- Infections including potentially life threatening infections
- Muscle aches
- Muscle weakness
- Joint swelling or achiness
- Dry or itchy skin
- Blushing or redness to face (flushing)
- Decreased function of the thyroid gland, which can result in feeling tired and weight gain that may first show up as an increased levels of thyroid stimulating hormone (hypothyroidism). If your thyroid function becomes abnormal, your doctor may have you take a thyroid replacement pill daily.
- Difficulty emptying the bladder (urinary retention)
- Pelvic pain
- Rash
- Throwing up (vomiting)
- Decreased sodium levels in the blood (hyponatremia)
- Abnormally high calcium in the blood stream, that can result in fatigue, confusion, feeling sick to your stomach, throwing up, difficulty passing stool, abnormal heartbeat, coma, and death (hypercalcemia)
- Abnormally low calcium in the blood stream, that can result in muscle cramps, abdominal cramps, spasms (hypocalcemia)
- Abnormal levels of potassium in the blood (hyper- or hypokalemia)
- Death
- Excessive sweating (hyperhidrosis)
- High blood sugar (hyperglycemia)
- Gastrointestinal bleeding
- Airway and lung infection (bronchopneumonia)
- Shingles (Herpes zoster)
- Severe infection secondary to low neutrophil count (neutropenic sepsis)

- Respiratory tract infection
- Elevated liver enzyme (alanine aminotransferase elevation)
- Elevated liver function test
- Confusion
- Depressed level of consciousness
- Drop in blood counts resulting in anemia, low white blood cell count (leucopenia), and low platelet count (thrombocytopenia) (pancytopenia)
- Spinning sensation (vertigo)
- Nosebleed (epistaxis)
- General physical health deterioration

**Rare but serious risks of pomalidomide** *(events occurring less than 2-3% of the time)*

- Chest wall pain
- Inability of the heart to properly pump blood to the lungs (right ventricular failure)
- Bleeding from the stomach large intestine and/or small intestine (gastrointestinal bleeding)
- Narrowing of the stomach or intestines (gastrointestinal stenosis)
- Chest pain that occurs when your heart doesn't get enough oxygen, which can be a warning sign of a heart attack (angina - unstable)
- An irregular heartbeat that results from the top/upper chambers of the heart “quivering” instead of beating normally (atrial fibrillation)
- Fast heart rate (tachycardia) or slow heart rate (bradycardia)
- Decrease in the ability of the heart to pump blood, because of weakening of the heart muscle (congestive heart failure)
- Lack of oxygen to the heart muscle which can cause damage to the heart (heart attack)
- Feeling like your heart is “fluttering or skipping” (heart palpitations)
- Bleeding in the brain (cerebral hemorrhage)
- Lack of oxygen to the brain caused by either bleeding in the brain or blood clot. Also called a stroke (cerebral vascular accident)
- Memory impairment
- Blood creatinine increased
- Excessive or abnormal loss of body fluids (dehydration)
- Failure to thrive
- Anxiety
- Feeling sad or blue (depression)
- Difficulty falling or staying asleep (insomnia)
- Changes in mood
- Kidney stones (nephrolithiasis)
- Collection of fluid in the space around the lung (pleural effusion)
- Inability of the lungs to function properly (respiratory failure)
- High blood pressure (hypertension) or low blood pressure (hypotension)
- Acute inflammation of the liver including hepatitis, liver failure, jaundice (yellowing of skin and whites of eyes) (hyperbilirubinemia)
- Inflammation of the lungs (interstitial lung disease)

- Possible second cancer with prolonged use
- Blurred vision
- Decreased level of phosphorus in the blood (hypophosphatemia)
- Decreased albumin in the blood (hypoalbuminemia)
- Low levels of magnesium in the blood (hypomagnesemia)
- Night sweats
- Changes in the voice or hoarseness (dysphonia)
- Nose bleed (epistaxis)
- Very sleepy, difficulty arousing (lethargy)
- Fainting (syncope)
- Excessive sleepiness (somnolence/depressed level of consciousness)
- Change in taste sensation (dysgeusia)
- Dry mouth
- Chills
- Recurrent areas of skin or mucosal swelling of sudden onset, usually disappearing within 24 hours; an allergic reaction to the medication (angioedema) an exaggerated or inappropriate immune response (hypersensitivity) to pomalidomide
- Hepatitis B viral activation
- Kidney failure and blood chemistry abnormalities secondary to destruction of cancer cells by anti-cancer treatment (tumor lysis syndrome)
- Skin cancer (basal cell carcinoma and squamous cell carcinoma)
- Development of a new cancer during cancer treatment (secondary primary malignancies) including blood and bone marrow cancers (Hematologic malignancies), solid organ tumors (solid tumors), and skin cancers.
- Inflammation of the lungs (pneumonitis)

ANIMAL STUDIES
In one study, a monkey developed a condition compatible with acute myelogenous leukemia after receiving high doses of pomalidomide for several months. The cause of this effect is being investigated and the risk of this finding to humans is unknown.

As with any medication, allergic reactions are a possibility.

**Standard of Care Risks**
Your doctor will discuss the risks of biopsies, X-rays, scans, and blood and urine testing *[include any tests/procedures performed as part of the participant's standard care]* as these tests and procedures are part of your standard clinical care.

**General risks**
The risks of drawing blood include pain, bruising, or rarely infection at the needle site.

For more information about risks and side effects, ask your study doctor.

Risks Associated with Pregnancy

Pomalidomide is related to thalidomide. Thalidomide is a known to cause severe life-threatening human birth defects. If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females must not become pregnant while taking pomalidomide. You have been informed that the risk of birth defects is unknown. If you are female, you agree not to become pregnant while taking pomalidomide.

Pomalidomide is detected in trace quantities in human semen according to a study. The risk to the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time. For these reasons male patients receiving pomalidomide must use a latex condom while taking pomalidomide, when temporarily stopping pomalidomide, and for 90 days after permanently stopping pomalidomide treatment during any sexual contact with a pregnant female or a female of child bearing potential even if you have undergone a successful vasectomy.

Patients should not donate blood during treatment therapy or for 28 days following discontinuation of pomalidomide.

You must **NEVER** share pomalidomide with anyone else.

**POTENTIAL DISCOMFORTS AND RISKS OF DEXAMETHASONE**

**Likely risks of dexamethasone:**

- Stomach and throat ulcers or worsening of any ulcers you had before treatment
- Swelling and pain of the pancreas
- Weight gain around the stomach
- Puffiness (especially in the face)
- Buildup of fluids and a rise in blood pressure
- Possible rise in your blood sugar
- Changes in the blood levels of potassium.
- Infection

**Less likely risks of dexamethasone:**

- Muscle weakness
- Brittle bones
- Menstrual changes
- Itching, and other allergic reactions, some severe.

**Rare but serious risks of dexamethasone:**

- Mood swings
- Depression
- Trouble sleeping
- Changes in personality
- Seizures
- Dizziness
- Patients who are more likely to get heart disease may have heart failure

**BIRTH CONTROL, DANGERS OF PREGNANCY AND BREASTFEEDING**

You must not get pregnant while in this study. If you are or become pregnant, there may be unknown risks to the baby. If you may be able to have children, you will be given a pregnancy test at screening, and if the result is positive, you will not be able to be in the study. If you are sexually active, and able to have children, you and your partner must use two (2) highly effective forms of birth control throughout the study and for 90 days after your last dose of study drugs.

Acceptable non-hormonal birth control methods include:

- Total sexual abstinence. Abstinence must be for the total duration of the study i.e. from when you sign the informed consent form (ICF) until 90 days after the last dose of study drugs
- Male sexual partner who has undergone a vasectomy plus male condom with spermicide. (You will need to confirm that your partner's sperm was tested after the vasectomy procedure and that he was confirmed to be sterile.)
- Tubal occlusion plus male condom with spermicide
- Intrauterine Device (IUD) plus male condom with spermicide

Acceptable hormonal methods include:

- Etonogestrel implants (e.g., Implanon®, Norplan®) plus male condom with spermicide
- Normal and low dose combined oral pills plus male condom with spermicide
- Norelgestromin/ethinyl estradiol (EE) transdermal system plus male condom with spermicide
- Intravaginal device (e.g., EE and etonogestrel) plus male condom with spermicide
- Cerazette® (desogestrel) plus male condom with spermicide. (Cerazette® is currently the only highly efficacious progesterone based pill.)

You should discuss with your study doctor which birth control methods are considered acceptable.

A pregnancy test can be wrong. If you become pregnant or think you may be pregnant during the study, stop taking study capsules and contact the study doctor's office **immediately**. You will be asked to withdraw from the study. You must not be breast-feeding an infant during the study. The study drug may cause unforeseeable risk to a breastfed baby. The study doctor must follow up and document the course and the outcome of all pregnancies, even if you withdraw from the study or if the study has finished.

**OTHER RISKS**

Additionally, you might also have side effects or discomforts that are not listed in this form. Some side effects are not yet known, and every risk or side effect cannot be predicted. You may experience unexpected side effects or be at risk for symptoms, illnesses, and/or complications that could not be predicted. Tell your study doctor or study staff right away if you have any problems.

Many side effects go away shortly after the study drugs are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death. Some

side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

**Standard of care risks**
Your doctor will discuss the risks of biopsies, X-rays, PET/CT and MRI scans, and blood and urine testing, as these tests and procedures are part of your standard clinical care.

**Blood Samples**
Blood samples will be taken using a needle from a vein in your arm during the study. The taking of a blood sample may cause some discomfort and bruising, and there is a potential for infection. Other risks, although rare, include dizziness and fainting. The maximum amount of blood that will be taken at any study visit is about 42 mL (less than 3 tablespoons).

Blood loss from taking research samples and the side effects of the study drug may cause anemia (low red blood cell count). Anemia may make you feel tired. Some people may need iron supplements to compensate for the blood loss resulting from the procedures done during this study. Please make sure that you discuss this with the study doctor or your personal doctor.

**Non-Physical Risks**
You may lose time at work or home and spend more time in the hospital or study doctor's office than usual.

**Genetic Testing**
This study involves testing your DNA, which is the genetic information you inherited from your parents (also known as genetic testing). You will not be notified of the genetic test results and they will not be put into your medical record.

## 7. Are there reasons you might leave this research study early?

Taking part in this research study is your decision. You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In addition, the Principal Investigator, the companies supplying the drugs and funding or the medical institution may stop you from taking part in this study at any time:

- If it is in your best clinical interest,
- If you do not follow the study procedures,
- If the study is stopped.

If you leave this research study early, or are withdrawn from the study, no more information about you will be collected; however, information already collected about you in the study may continue to be used.

## 8. What if you are injured from your participation in this research study?

**Where to get help:**

If you think you have suffered a research-related injury, you should promptly notify the Principal Investigator listed in the Contact Information at the beginning of this form.

**Who will pay for the treatment of research related injuries:**

Care for such research-related injuries will be billed in the ordinary manner, to you or your insurance. You will be responsible for all treatment costs not covered by your insurance, including deductibles, co-payments and coinsurance. The study will not offer free medical care or payment for any bad side effects from taking part in this study.

## 9. What are the possible benefits from being in this research study?

This study may not make your health better. If you agree to take part in this study, there may or may not be direct medical benefit to you. We hope the information learned from this study will benefit other people with multiple myeloma in the future.

## 10. What alternative do you have if you choose not to participate in this research study?

You do not have to be in this study to receive treatment for your condition. Your other choices may include:

- Taking part in another study
- Getting treatment or care for your cancer without being in a study
- Getting no treatment

You should talk to the researcher and your regular physician about each of your choices before you decide if you will take part in this study.

## 11. What tests or procedures will you need to pay for if you take part in this research study?

The study drugs, ixazomib and pomalidomide, will be given to you at no cost. You and/or your insurance might also have to pay for other drugs or treatments given to help control side effects.

You won't need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Research testing on your blood and bone marrow
- Research testing on any biopsy tissue

You and/or your insurance will need to pay for all other tests and procedures that are part of this research study because they are part of usual care for your cancer. Before you take part in this study, you should call your insurer to find out if the cost of these tests and/or procedures will be covered. You will have to pay for any costs not covered by your insurance.

**If you have billing or insurance questions call Research Billing at the telephone number provided in the Contact Information section of this form.**

## 12. Will you be paid for taking part in this research study?

You will not be paid for taking part in this study.

Your participation in this research study may contribute to the development of commercial products from which Takeda/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.

## 13. What will happen to your samples?

Your samples will be sent to the Sponsor (Mayo Clinic). The Sponsor can use your samples for research purposes only as described in the research study and this consent form. Your sample will be sent to the Sponsor in a coded format, which protects your identity. Mayo Clinic may destroy the sample at any time without telling you.

## 14. How will your privacy and the confidentiality of your records be protected?

*[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]*

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Mayo Clinic, the sponsor of this study
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- Takeda Pharmaceuticals/Millennium Pharmaceuticals, Celgene Corporation, and the Multiple Myeloma Research Foundation and Consortium (MMRF/MMRC)

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.

*[Note to Local Investigators: The NCI has recommended that the above paragraph, containing language required by the FDA, be added in order to be in compliance with the Final Rule by the effective date of 07Mar2012.]*

## ENROLLMENT AND PERMISSION SIGNATURES

**Your signature documents your permission to take part in this research.**

| | / / | : AM/PM |
|---|---|---|
| Printed Name | Date | Time |

Signature

**Person Obtaining Consent**

- I have explained the research study to the participant.
- I have answered all questions about this research study to the best of my ability.

| | / / | : AM/PM |
|---|---|---|
| Printed Name | Date | Time |

Signature

*Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the North Central Cancer Treatment Group Operations Office for approval before a patient may be registered to this study.*

*Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.*