Mayo Clinic Cancer Center

Phase 2 Trial of Induction with Ixazomib, Pomalidomide, Dexamethasone Prior to Salvage Autologous Stem Cell Transplantation followed by Consolidation with Ixazomib, Pomalidomide, and Dexamethasone and Ixazomib Maintenance in Multiple Myeloma

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Takeda Study: X16067

Drug Availability
Commercial Agents: Dexamethasone, Pomalidomide
Drug Company Supplied: Ixazomib (**Takeda**) (IND# 135102)

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Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/ interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
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Serious Adverse Events	[redacted]
Biospecimens	[redacted]

*No waivers of eligibility per NCI

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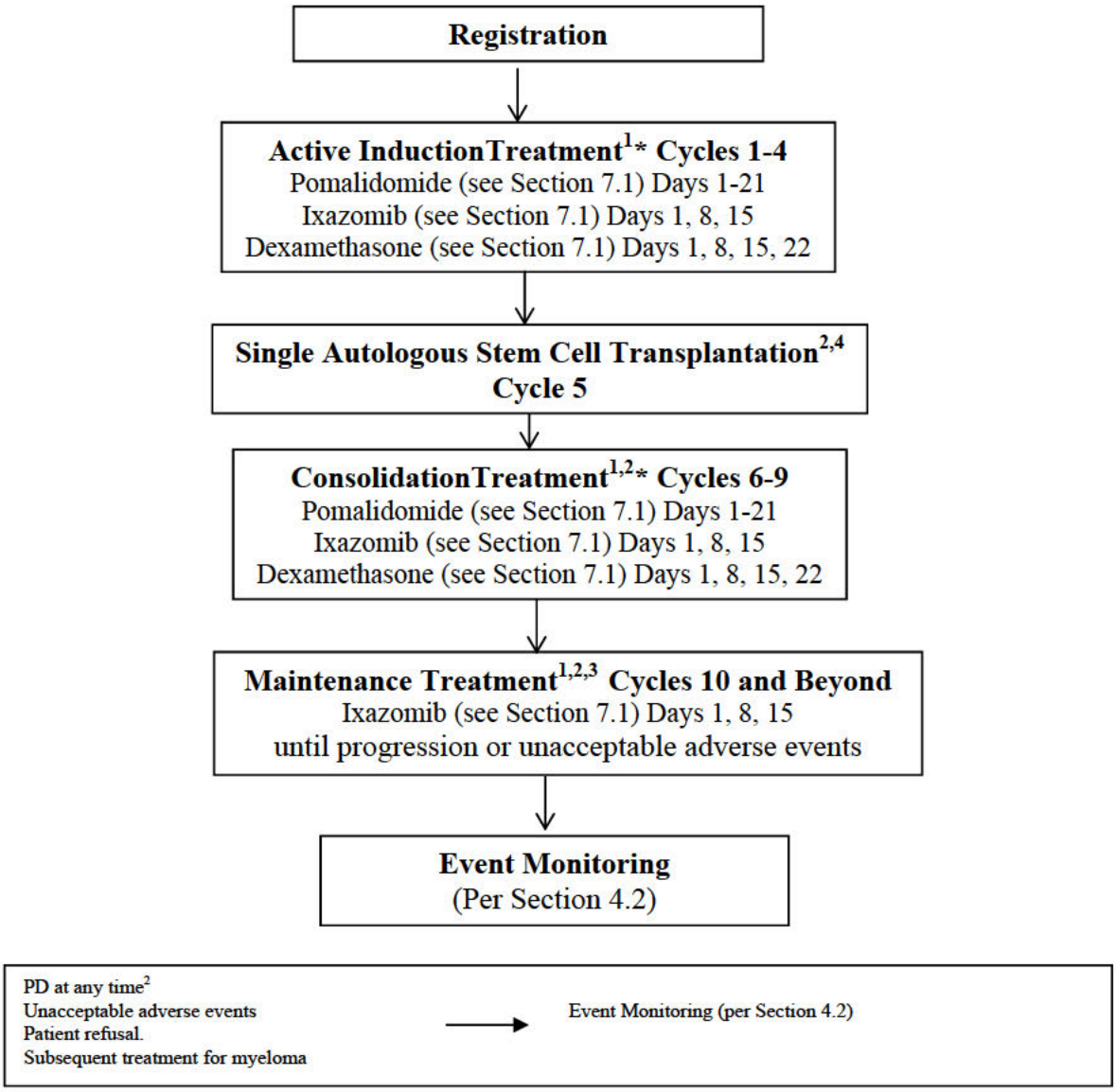
Schema



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

[1]Cycles 1-3 length = 28 days
Cycle 4 length = up to 56 days
Cycle 5 length = up to 120 days
Cycles 6-8 length = 28 days
Cycle 9 length = up to 56 days
Cycles 10 and beyond length = 28 days

[2] Window period is 2-4weeks between Induction and ASCT; 60-120 days between ASCT and Consolidation and 0-4 weeks between the Consolidation and Maintenance phases.

[3] Confirmation of PD is not required. 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 Patient Status Form.

[4] Melphalan conditioning followed by stem cell infusion is being considered as 'cycle 5' for logistical reasons only. No additional toxicity data will be collected in the immediate post ASCT period until day 60-100 when the patient returns for routine post ASCT-reevaluation.

Generic name: Ixazomib Brand name(s): Ninlaro® Mayo Abbreviation: MLN9708 Availability: Takeda	Generic name: Dexamethasone Brand name(s): Decadron® Mayo Abbreviation: DXM Availability: Commercial	Generic name: Pomalidomide Brand name(s): Pomalyst® Mayo Abbreviation: CC4047 Availability: Commercial via POMALYST REMS™ program

1.0 Background

1.1 ***Multiple Myeloma:*** Multiple myeloma (MM) 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 27,000 patients with myeloma are diagnosed in the United States each year (seer.cancer.gov), and despite considerable improvements in therapy remains incurable and uniformly fatal, with a median overall survival of around 6 years (Kumar SK et al. 2013). Recent improvements in therapies have significantly improved the survival outcomes (Kumar et al. 2013), but given the inevitable relapses seen in these patients, new approaches to therapy are clearly needed.

1.2 ***Implications of salvage ASCT approach in multiple myeloma***: The management of MM has witnessed a substantial change over the past decade, primarily as a result of the use of effective novel agents. Previously, the conventional approach for SCT-eligible patients was induction therapy with dexamethasone alone or combination regimens like Vincristine, Adriamycin, and Dexamethasone (VAD) for 4–6 months, followed by high-dose melphalan and peripheral autologous blood stem cell transplantation (SCT), as phase 3 trials had demonstrated a survival improvement with SCT approach compared to conventional chemotherapy, initially in patients younger than 65 (Kyle RA, Rajkumar SV 2004, Attal M et al. 1996 . Child JA et al. 2003) and subsequently in SCT-eligible older patients as well. (Kumar SK. et al. 2008) Additionally, one randomized trial demonstrated comparable efficacy for SCT applied early in the course of the disease course or when used as salvage therapy following failure of primary therapy (Fermand JP et al, 1998).

With the use of well-tolerated novel agents in combinations with dexamethasone, or with other conventional agents, response rates comparable to those witnessed in the context of SCT were noted (Rajkumar SV et al 2008., Harousseau JL et al. 2007. Cavo M, et al 2009). Therefore, the advantages seen with early SCT have somewhat diminished and many patients prefer to defer SCT until relapse. (Lacy et al 2007, Rajkumar et al. 2008) The preliminary data analysis of the IFM/DFCI DETERMINATION trial showed no improvement in overall survival (OS) in patients who were randomized to early SCT underscoring again that SCT may be deferred in the context of current regimens (Attal M. et al. , 2015) . The theories that patients relapsing after induction with a novel agent-based regimen will not be able to obtain a meaningful response from high-dose melphalan and that patients will be losing the opportunity to benefit from an effective treatment modality such as SCT have largely been debunked. In fact comparisons of patients going to early SCT to those who decided to stay on initial therapy in recent clinical trials have suggested favorable survival outcomes for both groups (Kumar SK et al., 2012)

Autologous stem cell transplantation (ASCT) is increasingly being used as salvage therapy in patients with relapsed and refractory multiple myeloma. While utility of this approach has not been studied in a prospective fashion, sufficient evidence exists from retrospective studies to consider this therapy in patients with relapsed disease. It has been used as an effective salvage treatment, both for patients who have not had a prior transplant as well as those who have received a single ASCT as part of their initial treatment.

The International Myeloma Working Group in collaboration with the Blood and Marrow Transplant Clinical Trials Network, the American Society of Blood and Marrow Transplantation, and the European Society of Blood and Marrow Transplantation recently summarized current knowledge regarding the role of ASCT in MM patients progressing

after primary therapy and proposed guidelines for the use of salvage HCT in MM. (Giralt et al, 2015). The expert committee recommended that salvage ASCT should be considered standard in transplantation-eligible patients relapsing after non SCT-based primary therapy and that the role of post salvage ASCT maintenance needs to be explored in the context of well-designed prospective trials that should include new agents, such as monoclonal antibodies, immune-modulating agents, and oral proteasome inhibitors (Giralt et al, 2015). Reinduction treatment with combination chemotherapy is the standard and most experts agree that high-dose therapy consolidation should be considered the standard of care at this time for this patient population. The experts agreed that this patient population of relapsed/refractory myeloma, although heterogeneous, is worthy of prospective trials designed to address the issue of optimal reinduction therapy and consolidation to determine whether their natural history is different than that for patients relapsing after a prior autograft. (Giralt et al. 2015).

The Mayo Clinic Group retrospectively studied 290 patients with untreated MM who received IMiD-based initial therapy (Kumar S et al., 2012) Patients who underwent a stem cell harvest attempt were considered transplantation-eligible and were included. SCT within 12 months of diagnosis and within 2 months of harvest were considered early SCT (n=173). SCT >12 months after diagnosis was considered delayed SCT (n=112). In the delayed SCT group, 42 patients had undergone SCT, and the median estimated time to SCT was 5.3 months and 44.5 months in the early SCT and delayed SCT groups, respectively. The 4-year overall survival rate from diagnosis was 73% in both groups. The time to progression after SCT was similar between the early and delayed SCT groups. These results indicated that, in transplantation-eligible patients who receive IMiDs as initial therapy followed by early stem cell mobilization, delayed SCT results in similar overall survival compared with early SCT (Kumar S et al., 2012).

Although, the introduction of newer, more effective therapies such as IMiDs and the proteasome inhibitor bortezomib has led to high response rates and deeper responses and has raised questions regarding the continued role of SCT in this disease, MM remains the most common indication for ASCT in North America according to data reported to the CIBMTR. The results of the S9321 trial suggested that the survival advantage of upfront SCT might not persist once the complete response rates of conventional therapy improved (Barlogie et al., 2006). As a result of the high response rates seen at the end of the induction therapy, and low toxicity profile of current regimens, patients are increasingly opting to delay SCT and continue with initial therapy. (Rajkumar et al., 2008, Lacy et al, 2007)

The Mayo Clinic study showed that the paradigm of comparable survival with early or delayed-SCT holds true in the context of newer therapies as it did with the alkylator based regimens of the past. The results were true irrespective of the specific IMiD used, whether thalidomide or lenalidomide, further confirming that the equivalence of SCT used in an early or deferred fashion is therapy independent. The differences in proportion of patients on the two drugs in the two groups likely reflects the better tolerability of lenalidomide and the increasing comfort on the part of physicians to defer transplant with the availability of more long term data with lenalidomide. (Kumar S, 2012). The comparable time to progression after early or delayed-SCT was in stark contrast to the results from the previous randomized trials that examined early versus delayed-SCT. In the MAG90 trial, a delayed-SCT was associated with a shorter TTP after SCT even though the overall survival was comparable with the two approaches (Fermand JP et al, 1998).

An aspect of the early transplant approach that was traditionally used to favor an early transplant had been the reduced time with symptoms and side effects of therapy. However, this paradigm has been changed with the newer agents, which are much better tolerated and can often be continued for prolonged duration with minimal toxicity and impact on quality of life. Hence it is not surprising that there is increased acceptance of the delayed-SCT approach. This will have to be explored in the context of prospective trials comparing an early-SCT to delayed-SCT. The decision to go ahead with an early SCT or to defer transplant till relapse can be based on several factors including response to induction therapy, toxicity from treatment, physician bias, and patient perception among others. The Mayo study addressed the use of SCT primarily as the second line of therapy, as was the common practice in the period that was studied, and the results cannot be necessarily extrapolated to patients receiving an SCT after failing multiple lines of therapy with different newer drugs (Kumar S, 2012).

In another study, the Mayo Clinic Group examined the outcomes in 98 patients undergoing salvage ASCT for relapsed MM after receiving an initial transplant. (Gonsalves W. et al., 2013). The median age at second ASCT was 60 years and the median time between the two ASCTs was 46 months. The median PFS from ASCT was 10.3 months and the median OS was 33 months. In a multivariable analysis, a shorter time-to-progression (TTP) after initial ASCT, not achieving a CR after salvage ASCT, higher number of treatment regimens before second ASCT and a higher plasma cell labeling index at ASCT, predicted for shorter PFS. However, only a shorter TTP after first ASCT predicted for a shorter OS. From this study as well as the prior studies in the literature, it is clear that salvage ASCT is an effective and feasible therapeutic option for MM patients relapsing after other treatments.

Investigators at the University of Arkansas, reported on 94 patients who had relapsed following ASCT, 31 of whom received a second ASCT at relapse. (Tricot G. et al., 1995) In this study, patients receiving a second autologous or allogeneic transplant had a better survival compared to those who received standard therapy, which may also reflect patient selection. Patients with low beta-2-microglobulin or a response lasting more than 12 months from the first ASCT had better survival with salvage therapy.

A group of investigators from the UK studied 172 patients who relapsed after one ASCT that was performed at maximal response from induction therapy with CVAMP regimen. (Alvares et al., 2006) Among these, 118 patients received CVAMP at relapse and 54 received alternative chemotherapy followed by a second ASCT in 83 of them, based on availability of stem cells and performance status. No difference was seen in EFS for patients receiving a second ASCT or alternative therapy at first relapse though there was a trend towards improved OS with repeat ASCT. In this study, there was no benefit to a second ASCT in those patients whose response from the initial transplant lasted less than 18 months with a median survival of less than six months compared to nearly 3 years for those with longer response duration from the first transplant.

Another study reported on patients who had up-front ASCT followed by a second ASCT in case of relapse or progression (Elice et al., 2006). Among the 70 patients who relapsed, 26 went on to have a second ASCT at a median time of 20.4 months from first ASCT. Median OS and EFS after the second ASCT were 38.1 and 14.8 months.

Studies have not systematically studied the impact of induction therapy prior to salvage ASCT or the role of post-transplant consolidation and maintenance. While the responses to the salvage transplant is overall encouraging, it still remains rather short and approaches such as consolidation and maintenance that have improved outcomes in the

setting of initial transplant should be evaluated in the context of salvage transplant. The combination of a proteasome inhibitor and an IMiD is one of the most effective treatment regimens in MM(Richardson PG et al., 2010, Richardson PG, 2009).The 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. Some of these regimens require IV or subcutaneous administration, which can require frequent clinic, visits for patients.

Ixazomib is the first oral proteasome inhibitor to enter the clinic and has efficacy similar to bortezomib, with excellent activity seen in combination with lenalidomide in the setting of newly diagnosed disease. Pomalidomide is a new IMiD with activity seen in nearly a third of the patients who are refractory to lenalidomide. The combination offers a convenient oral regimen that is also a potentially effective combination in patients with relapsed disease who would have been exposed to prior IMiDs and proteasome inhibitors. The oral proteasome inhibitor also offers the opportunity to study a convenient maintenance therapy in the setting of relapsed disease. The current study proposes to examine the outcome following a salvage stem cell transplant, done following an effective induction therapy, and followed by consolidation and maintenance.

1.3 ***Ixazomib***: MLN9708, 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. In water or aqueous systems, MLN9708 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 MLN9708. 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 citrate (MLN9708). 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.

In Vivo Pharmacology: 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.

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

In Vivo Toxicology: 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. 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: 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. 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.

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, clinical pharmacology studies have evaluated drug-drug interactions with ketoconazole, clarithromycin, and rifampin, as well as the effect of food, renal impairment, and hepatic impairment on the PK of ixazomib. Studies evaluating the safety and pharmacokinetics (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 RRMM 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.

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

Pharmacokinetics and Drug Metabolism: After oral dosing, absorption of ixazomib is rapid with a median first time to maximum observed plasma concentration (Tmax) of approximately 1 hour postdose. The plasma exposure (AUC) of ixazomib increases in a dose-proportional manner over a dose range of 0.2 to 10.6 mg based on population PK analysis. The absolute oral bioavailability (F) of ixazomib is estimated to be 58% based on population PK analysis. A high-fat meal reduced ixazomib Cmax by 69% and AUC0-216 by 28%. This indicates that a high-fat meal decreases both the rate and extent of absorption of ixazomib. Therefore, ixazomib should be dosed at least 2 hours after food or 1 hour before food.

The steady-state volume of distribution of ixazomib is large and is estimated to be 543 L based on a population PK model. Based on in vitro plasma protein binding measurements on samples from clinical studies (Studies C16015 and C16018), ixazomib is highly bound to plasma proteins (99%). Ixazomib concentrations are higher in whole blood than in plasma, indicating extensive partitioning of ixazomib into red blood cells, which are known to contain high concentrations of the 20S proteasome.

Metabolism appears to be the major route of elimination for ixazomib. In vitro studies indicate that ixazomib is metabolized by multiple cytochrome P450 (CYP) and non-CYP proteins. At concentrations exceeding those observed clinically (10 μM), ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42.3%), 1A2 (26.1%), 2B6 (16.0%), 2C8 (6.0%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (<1%). At 0.1 and 0.5 μM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg ixazomib, non-CYP mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. These data indicate that at clinically relevant concentrations of ixazomib, non-CYP proteins contribute to the clearance of ixazomib and no specific CYP isozyme predominantly contributes to the clearance of ixazomib. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor would be expected.

Ixazomib is neither a time-dependent inhibitor nor a reversible inhibitor of CYPs 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. Ixazomib did not induce CYPs 1A2, 2B6, and 3A4/5 activity or corresponding immunoreactive protein levels. Thus, the potential for ixazomib to produce DDIs via CYP isozyme induction or inhibition is low.

Ixazomib is not a substrate of BCRP, MRP2 and OATPs. Ixazomib is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1 and MATE2-K. Ixazomib is unlikely to cause or be susceptible to clinical DDIs with substrates or inhibitors of clinically relevant drug transporters.

The geometric mean terminal half-life ($t_{1/2}$) of ixazomib is 9.5 days based on population PK analysis. For both IV and oral dosing, there is an approximately average 3-fold accumulation (based on AUC) following the Day 11 dose for the twice-weekly schedule

and a 2-fold accumulation (based on AUC) following the Day 15 dose for the once-weekly schedule.

Mean plasma clearance (CL) of ixazomib is 1.86 L/hr based on the results of a population PK analysis. Taken together with the blood-to-plasma AUC ratio of approximately 10, it can be inferred that ixazomib is a low clearance drug. Using the absolute oral bioavailability (F) estimate of 58% (also from a population PK model), this translates to an apparent oral plasma clearance (CL/F) of 3.21 L/hr. The geometric mean renal clearance for ixazomib is 0.119 L/hr, which is 3.7% of CL/F and 6.4% of CL estimated in a population PK analysis. Therefore, renal clearance does not meaningfully contribute to ixazomib clearance in humans. Approximately 62% of the administered radioactivity in the ADME study (Study C16016) was recovered in the urine and 22% of the total radioactivity was recovered in the feces after oral administration. Only 3.2% of the administered ixazomib dose was recovered in the urine as unchanged ixazomib up to 168 hours after oral dosing, suggesting that most of the total radioactivity in urine was attributable to metabolites.

The PK of ixazomib was similar with and without co-administration of clarithromycin, a strong CYP3A inhibitor, and hence no dose adjustment is necessary when ixazomib is administered with strong CYP3A inhibitors. Consistently, in a population PK analysis, co-administration of strong CYP1A2 inhibitors did not affect ixazomib clearance. Therefore, no dose adjustment is required for patients receiving strong inhibitors of CYP1A2. Based on information from the clinical rifampin DDI study, ixazomib C_{max} and $AUC_{0\text{-last}}$ were reduced in the presence of rifampin by approximately 54% and 74%, respectively. Therefore, the co-administration of strong CYP3A inducers with ixazomib is not recommended.

Mild or moderate renal impairment (CrCL ≥ 30 mL/min) did not alter the PK of ixazomib based on the results from a population PK analysis. As a result, no dose adjustment is required for patients with mild or moderate renal impairment. In a dedicated renal impairment study (C16015), unbound AUC0-last was 38% higher in patients with severe renal impairment or ESRD patients requiring dialysis as compared to patients with normal renal function. Accordingly, a reduced starting dose of ixazomib is appropriate in patients with severe renal impairment or ESRD requiring dialysis. Pre- and post-dialyzer concentrations of ixazomib measured during the hemodialysis session were similar, suggesting that ixazomib is not readily dialyzable, consistent with its high plasma protein binding (99%).

The PK of ixazomib is similar in patients with normal hepatic function and in patients with mild hepatic impairment, as defined by the National Cancer Institute Organ Dysfunction Working Group (total bilirubin <1.5 times the upper limit of normal [ULN]), based on the results from a population PK analysis. Consequently, no dose adjustment is required for patients with mild hepatic impairment. In a dedicated PK study in patients with moderate (total bilirubin >1.5 to 3 times the ULN) or severe (total bilirubin >3 times the ULN) hepatic impairment (Study C16018), unbound dose-normalized $AUC_{0\text{-last}}$ was 27% higher in patients with moderate or severe hepatic impairment as compared to patients with normal hepatic function. Therefore, a reduced starting dose of ixazomib is appropriate in patients with moderate or severe hepatic impairment.

There was no statistically significant effect of age (23-91 years), sex, body surface area (1.2-2.7 m^2), or race on the clearance of ixazomib based on the results from a population PK analysis.

Further details on these studies are provided in the IB.

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

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m^2) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose[a] W
C16010	PO, W, with LenDex versus	4.0 mg W

Table 1-1 Clinical Studies of Oral Ixazomib

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

Abbreviations: RRAL = Relapsed and/or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area; Dex=dexamethasone; DLT = dose-limiting toxicity; IV = intravenously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RR= relapsed and/or refractory; RRAL= relapsed and/or

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated

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 Preferred Term	Oral Single Agent Total n=201 (n%)
Subjects with at Least One Adverse Event	**197 (98)**
Gastrointestinal disorders	**160 (80)**
Nausea	**106 (53)**
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)**

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

Primary System Organ Class Preferred Term	Oral Single Agent Total n=201 (n%)
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)
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 that have completed enrollment or are actively enrolling patients with multiple myeloma to investigate oral ixazomib in combination with standard combination regimens. The most frequent (at least 10%) AEs occurring in the pooled safety population from Studies C16005, C16006, C16008, and C16013 are shown for all grades (Table 1-3). Note that in combination trials, "related" is defined as related to any study drug in the combination regimen.

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

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 (n%)
Subjects with at Least One Adverse Event	**163 (94)**
Gastrointestinal disorders	**139 (80)**
Nausea	**65 (38)**
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)**

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

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 (n%)
Anemia	**45 (26)**
Neutropenia	**43 (25)**
Lymphopenia	**20 (12)**
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)

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

Relapsed and/or Refractory Multiple Myeloma:

Please refer to the ixazomib IB for further information.

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 a 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 relapsed/refractory myeloma need newer therapies. The combination of pomalidomide and ixazomib provides a potentially powerful combination due to several reasons. Studies have not systematically studied the impact of induction therapy prior to salvage ASCT or the role of post-transplant consolidation and maintenance. While the responses to the salvage transplant is overall encouraging, it still remains rather short and approaches such as consolidation and maintenance that have improved outcomes in the setting of initial transplant should be evaluated in the context of salvage transplant. The combination of a proteasome inhibitor and an IMiD is one of the most effective treatment regimens in MM as has been seen with bortezomib or carfilzomib combinations with thalidomide or lenalidomide.[6-8] A recently described mechanism of action of lenalidomide includes increased protein ubiquitination and brings into question mechanism of synergy between IMiDs and proteasome inhibitors. Despite this paradoxical preclinical data, clinical experience supports their synergistic activity.

Ixazomib is the first oral proteasome inhibitor to enter the clinic and has efficacy similar to bortezomib, with excellent activity seen in combination with lenalidomide in the setting of relapsed refractory MM in a recently reported phase 3 trial (TOURMALINE-MM1 study) (reference ASH abstract 2015 Moreau) . Pomalidomide is new IMiD with activity seen in nearly a third of the patients refractory to lenalidomide. The combination offers a convenient oral regimen that is also a potentially effective combination in patients with relapsed disease who would have been exposed to prior IMiDs and proteasome inhibitors. The oral proteasome inhibitor also offers the opportunity to study a convenient maintenance therapy in the setting of relapsed disease.

The current study proposes to examine the outcome following a salvage stem cell transplant, done following an effective induction therapy, and followed by consolidation and maintenance.

1.7 Potential Risks and Benefits of ixazomib

Please refer to the current ixazomib IB.

The clinical benefit of ixazomib continues to be studied in a comprehensive and global development plan that involves studies sponsored by Takeda. Ixazomib appears to show early signs of anti-tumor activity as evidenced by at least 50% reduction in disease

burden in some patients, including patients that have been heavily pretreated as well as those with newly diagnosed MM, and prolongs stabilization of the underlying disease in other patients across all ongoing trials. The preliminary findings are favorable when considering historical and currently available therapies for the patient populations evaluated. Though additional data are needed to characterize the clinical benefit of this drug, the emerging data support expanded development of ixazomib for the treatment of patients with advanced malignancy.

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2.0 Goals

2.1 Primary

To estimate the rate of progression free survival at 18 months from study entry after therapy with Ixazomib (MLN9708) in combination with pomalidomide and dexamethasone followed by a single ASCT and consolidation with ixazomib in combination with pomalidomide and dexamethasone and maintenance with ixazomib in relapsed refractory ASCT naïve MM patients.

2.2 Secondary

2.21 To determine the best overall response rates (≥ PR) and deep responses (VGPR, CR, sCR) at various stages of treatment: after induction, after SCT, after consolidation and during maintenance.

2.22 To determine the overall survival from study entry.

2.3 Correlative Research

2.31 Assessment of minimal residual disease (MRD) by flow cytometry at various stages of treatment: after induction, day # 100 after SCT, after consolidation and during maintenance at year 1 and 2 from initiation of maintenance therapy

2.32 To determine the engraftment kinetics (WBC and platelet) following single salvage ASCT for relapsed disease

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Previously treated ASCT naïve MM patients, currently with relapsed or refractory disease who are being considered for single ASCT for relapsed disease. Patients must be eligible to undergo a stem cell transplant as per institutional criteria for selection at the time of registration.

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 ≥75x10^9/L unless the participant has ≥50% bone marrow infiltration in which case a platelet count of ≥50x10^9/L is allowed
- Hemoglobin ≥9.0 g/dL
- Total bilirubin ≤ 1.5 × the upper limit of the normal range (ULN) or if total bilirubin is >1.5 x ULN, the direct bilirubin must be ≤ 2.0 mg/dL.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN or <5 x ULN if liver involvement

*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:

- Serum monoclonal protein ≥1.0 g/dL by protein electrophoresis
- ≥200 mg of monoclonal protein in the urine on 24-hour electrophoresis
- Serum immunoglobulin free light chain ≥10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.

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

3.16 Willing to provide informed written consent.

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

3.18 Willing to follow strict birth control measures.

Persons of childbearing potential, agree to one of the following:

- Practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, AND must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Persons able to father a child: even if surgically sterilized (i.e., status post-vasectomy), must agree to one of the following:

- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Must also adhere to the guidelines of any treatment-specific pregnancy prevention program, if applicable, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

3.19a Negative human immunodeficiency virus (HIV), hepatitis B and C test.

3.19b Willing to follow the requirements of the Pomalyst REMS program.

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

3.19d Willing to provide bone marrow samples under IRB#521-93 for correlative research purposes (see Sections 6.2 and 14.0).

3.2 Exclusion Criteria

3.21 Diagnosed or treated for another malignancy ≤2 years prior to registration or previously diagnosed with another malignancy and have any evidence of residual disease.
NOTE: If there is a history or prior malignancy, patient must not be receiving other specific treatment for their cancer. Patients with non-melanoma skin cancer or carcinoma in situ of any type, or low-risk prostate cancer after curative therapy, are not excluded if they have undergone complete resection.
NOTE: Platelet transfusions to help patients meet eligibility criteria are not allowed ≤3 days prior to study registration.

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:

- Pregnant persons
- Nursing persons
- Persons of childbearing potential who are unwilling to employ adequate contraception

3.23 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens. **NOTE:** this includes uncompensated heart or lung disease.

3.24 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm. **NOTE:** Bisphosphonates are considered to be supportive care rather than therapy and are allowed while on protocol treatment.

3.25 Patient has ≥Grade 2 peripheral neuropathy, or Grade 1 with pain on clinical examination during the screening period.

3.26 Major surgery ≤14 days prior to registration.

3.27 Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital) or use of Ginkgo biloba or St. John's wort ≤14 days prior to registration.

3.28 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. **NOTE**: 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 allergy to any of the study medications, their analogues or excipients in the various formulations.

3.29c Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of study treatment including difficulty swallowing.

3.29d Diarrhea >Grade 1, based on the NCI CTCAE v 4.0 grading, in the absence of antidiarrheals.

3.29e Failure to have fully recovered (ie, ≤Grade 1 toxicity) from the reversible effects of prior chemotherapy.

3.29f Radiotherapy ≤14 days prior to registration.
NOTE: If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the ixazomib.

3.29g Central nervous system involvement with disease under study (myeloma), or concurrent AL amyloidosis or plasma cell leukemia.

3.29hl Patients that have previously been treated with ixazomib, or participated in a study with ixazomib whether treated with ixazomib or not.

3.29i Prior stem cell transplantation for myeloma

4.0 Study Calendars

4.1 Test Schedule (excluding routine investigations in the peri-ASCT period*)

Tests and procedures	Prior to Registration ≤30 days	Prior to Registration ≤14 days	Induction and consolidation[16,1]	Every cycle pre-treatment including maintenance[1,7]	End of Cycle 4 of induction, post ASCT between Day 60-120, end of consolidation and 1 year post initiation of maintenance[1,14]	End of Treatment (±14 days)[1]
Complete medical history	X				X	
Adverse Event monitoring		X		X	X	X
Physical exam, including weight and vital signs		X		X	X	X
Height		X			X	
Performance status (ECOG scale)		X		X	X	X
Serum pregnancy test		X[11]				
CBC with differential		X	X[15]	X[15]	X	X
Chemistry group: sodium, potassium, glucose, alkaline phosphatase; total and direct bilirubin; SGOT (AST); SGPT (ALT), serum creatinine, calcium		X		X	X	X
HIV, hepatitis B and C	X					
LDH, $Beta_2$-microglobulin, C-reactive protein	X				X	
Electrophoresis of serum and urine (SPEP/UPEP)		X		X[3]	X	X[3]
Affected immunoglobulin[2]		X		X[2]	X	X[2]
Immunofixation serum and urine	X			X[4]	X	X[4]
Immunoglobulin free light chain (MML panel)		X		X[5]	X	X[5]
ECG	X					
X-ray skeletal survey or whole-body low-dose CT	X			X[6]	X[6]	X
CT Scan, PET/CT, or MRI for measurement if evidence of prior EMD lesion[8]	X			X[8]	X[8]	
Circulating plasma cell assessment (flow cytometry or peripheral smear)[9]		X		X[9]	X[9]	
Bone marrow aspirate and biopsy for myeloma[17]	X			X[10]	X[10]	X

Tests and procedures	Prior to Registration ≤30 days	Prior to Registration ≤14 days	Induction and consolidation[16,1]	Every cycle pre-treatment including maintenance[1,7]	End of Cycle 4 of induction, post ASCT between Day 60-120, end of consolidation and 1 year post initiation of maintenance[1,14]	End of Treatment (±14 days)[1]
Chest x-ray	X					
Register patient for POMALYST REMS™ program		X[12]				
Patient Medication Diary (Appendix II)[13]				X	X	X
Mandatory Research Bone marrow sample [18]	X[14]				X[14]	

*Performed per institutional guidelines. Melphalan conditioning followed by stem cell infusion is being considered as 'cycle 5' in the protocol for logistical reasons only. No additional toxicity data will be collected in the immediate post ASCT period until day 60-100 when the patient returns for routine post-ASCT reevaluation.

1) All scheduled visits are while patient is receiving therapy will have a window of ±7 days unless otherwise stated.
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) Every 365 days (12 months) or more often if clinically indicated.
7) Does not need to be repeated at Cycle 1 Day 1. Baseline values can be used for cycle 1.
8) This test is not mandatory. 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 suspected extra-medullary disease (EMD). Assessment of EMD lesions should be performed at end of induction, post ASCT (range:day 60-120), post consolidation (if persistent EMD noted previously) and every year on maintenance 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 and assess MRD. If a bone marrow was done to confirm CR prior to end of 4 cycles, no further bone marrow examination until the end of the phase (induction/~ day 100 post –ASCT, consolidation and annually while on maintenance if CR suspected).
11) For persons of childbearing potential only. Must be done ≤7 days prior to registration.

12) 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.

FOOTNOTES CONTINUE ON NEXT PAGE

13) The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution.
14) At baseline, end of the phase induction, ~ Day 100 post ASCT, end of consolidation, and 1 year after initiation of maintenance while on maintenance. See Section 14.0.
15) Can be performed at an outside facility
16) Induction Day 8, 15, 22 (Cycles 1-3), Day 15 (Cycle 4); consolidation Day 8, 15, 22 (Cycles 6-8), Day 15 (Cycle 9)
17) The following testing may be done if clinically indicated: Myeloma FISH, plasma cell proliferation, and flow cytometry (MRD).
18) Research blood and bone marrow collection per protocol IRB 521-93 will be done after consenting for 521-93 and according to that protocol. All processing will be done on Stabile 6.

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 **To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote 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 5:00 p.m. Central Time (Monday through Friday).**

The instructions for the registration/randomization application are available on the MCCC web page[redacted]) 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 and institution 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."

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

6.3 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.

6.4 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

6.5 Treatment on this protocol must commence at the recruiting institution under the supervision of a hematologist.

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

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

6.8 All required baseline symptoms (see Section 10.6) must be documented and graded.

6.9 Study drug is available on site.

7.0 Protocol Treatment

7.1 Cycle lengths:

Cycles 1-3 = 28 days
Cycle 4 = up to 56 days
Cycle 5 = up to 120 days
Cycles 6-8 = 28 days
Cycle 9 = up to 56 days
Cycles 10 and beyond = 28 days

7.2 Treatment Schedule

	Doses and Schedule				
	Agent	**Dose Level**	**Route**	**Day**	**Retreatment**
Cycles 1-4 Induction (x 4 cycles)	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
Cycle 5 Transplantation[a,e,f]	Stem cell mobilization[b] followed by single ASCT				
Cycles 6-9 Consolidation[c] (x 4 cycles)	Ixazomib	4 mg	PO	1, 8, 15	Every 28 days
	Pomalidomide	2 mg	PO	Days 1-21	Every 28 days
	Dexamethasone	40 mg	PO	1, 8, 15, 22	Every 28 days
Cycles 10 and Beyond Maintenance (until progression or unacceptable toxicity)[d]	Ixazomib	4 mg	PO	1, 8, 15	Every 28 days

a. **SCT**: Can be performed per institutional practice. Stem cells collected and cryopreserved ahead of time or collected immediately prior to transplant can be used. Conditioning regimen preference left to the treating physician, but should not be enrolled in any additional therapy trials.
b. If not previously collected and cryopreserved.
c If a patient previously has a dose reduction in induction, the consolidation phase will start and continue at reduced dose.
d. Ixazomib maintenance would start at 4 mg unless dose has been previously reduced in the Induction or consolidation phase due to a <u>non-hematologic toxicity</u> specifically attributed to Ixazomib.
e. Window period is 2-4weeks between Induction and ASCT; 60-120 days between ASCT and Consolidation and 0-4 weeks between the Consolidation and Maintenance phases.
f. Melphalan conditioning followed by stem cell infusion is being considered as ‘cycle 5’ for logistical reasons only. No additional toxicity data will be collected in the immediate post ASCT period until day 60-100 when the patient returns for routine post ASCT-reevaluation.

7.3 Dosing of ixazomib

The doses of ixazomib used in this study are based on data from Takeda'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).

7.4 How to take ixazomib

Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules The ixazomib should be taken on an empty stomach (no food or drink apart from 240 mL of water), at least 1 hour before or no sooner than 2 hours after food. 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.

7.5 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.

7.6 Treatment at enrolling institution

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.

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 4.2. 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 $\geq 1.0 \times 10^9$/L (=1000/microliter)
- The platelet count is $\geq 75 \times 10^9$/L unless the participant has ≥50% bone marrow infiltration in which case a platelet count of $\geq 50 \times 10^9$/L is allowed
- 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 below

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 (for each cycle during induction and consolidation and maintenance)

Table 8.2

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT#	ACTION**
Blood and lymphatic system disorders	Febrile neutropenia 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
Nervous System Disorders	Peripheral motor neuropathy OR Peripheral sensory neuropathy Newly developed Grade 1 with pain or ≥Grade 2	Ixazomib	Reduce dose of ixazomib to the next lower dose level
	Grade 2 with pain or Grade 3	Ixazomib	Omit ixazomib until AE resolves or returns to baseline. When AE resolves, re-initiate ixazomib at the next lower dose level.
	Grade 4	Ixazomib	Omit ixazomib. Peripheral neuropathy should be monitored until toxicity resolves or returns to baseline. 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
Skin and subcutaneous tissue disorders	Rash, maculo-papular Rash, acneiform Grade 2 or 3	Ixazomib	Omit ixazomib until rash resolves to ≤Grade 1 (See Section 9.9a). Restart at same dose. If the rash recurs, reduce dose by one dose level.
	Grade 4		Discontinue ixazomib

Table 8.2			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT[#]**	**ACTION****
Other	Any other non-hematological Grade 3 attributable adverse event except: Grade 3 nausea and/or emesis in the absence of optimal anti-emetic prophylaxis Grade 3 diarrhea that occurs in the absence of optimal supportive therapy Grade 3 fatigue (consider relatedness to one or all of the components of the combination)	Ixazomib Pomalidomide Dexamethasone	Omit ixazomib or pomalidomide or both depending on the attribution to either or both drugs, until resolution to Grade ≤1 or baseline. Restart at next lower dose - If a patient is already at the lowest drug level, go to event monitoring. 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.
Gastrointestinal Disorders			
General disorders and administration site conditions			
Other	Grade 4 Nonhematologic adverse events (consider relatedness to one or all of the components of the combination)	Ixazomib Pomalidomide Dexamethasone	Consider permanently discontinuing ixazomib or pomalidomide or dexamethasone or all three depending on the attribution to either one, two or all three drugs (exception would be if the investigator determines the patient is obtaining a clinical benefit) If both ixazomib and pomalidomide are discontinued, the patient will go to event monitoring.

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** 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 adverse events attributable to both ixazomib and pomalidomide, only one of the drugs should be reduced for each incidence of AEs 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

(For each cycle during induction and consolidation and maintenance)

Table 8.3

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Investigations	Neutrophil count decreased If ANC $<1.0 \times 10^9$/L or ANC $>1.0 \times 10^9$/L (up to LLN) with fever (temperature >38.5°C)	Pomalidomide	Omit pomalidomide dose. Follow CBC weekly. If neutropenia has resolved to ≤Grade 2 prior to Day 21 and fever has resolved, restart pomalidomide at next lower dose level and continue through Day 21of a 28-day cycle. 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	Platelet count decreased If platelet count $<30 \times 10^9$/L	Pomalidomide	Omit pomalidomide dose Follow CBC weekly Hold anticoagulation/antiplatelet therapy until platelets ≥50,000/mm³ If platelet count resolves to ≤Grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21 of each cycle
Skin and subcutaneous tissue disorders	Rash maculopapular Grade 2 or 3	Pomalidomide	Omit pomalidomide dose; follow weekly If the AE resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21of each cycle
	Grade 3-4 Stevens –Johnson Syndrome	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment
	≥Grade 3 Erythema multiforme	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment

Table 8.3			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Erythroderma ≤Grade 3	Pomalidomide	Omit pomalidomide dose; follow weekly If the AE resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21of the 28-day cycle
	Rash, maculo-papular Rash, acneiform Grade 4	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment
Nervous system disorders	Peripheral sensory neuropathy Grade 3	Pomalidomide	Omit pomalidomide dose and follow at least weekly. If the AE resolves to ≤Grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21of the 28-day cycle
	Peripheral sensory neuropathy 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 If the AE resolves to ≤Grade 1 prior to Day 15, restart at next lower dose level and continue through Day 21of the 28-day cycle
	Allergic reaction Grade 4	Pomalidomide	Discontinue pomalidomide and remove patient from all study treatment
Vascular disorders	Thromboembolic event ≥ Grade 3	Pomalidomide	Omit dose and start anticoagulation 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 See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.

Table 8.3			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Other non-hematologic adverse event	Other non-hematologic ≥Grade 3	Pomalidomide	If the AE 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 Omit pomalidomide dose. Follow at least weekly If the toxicity resolves to ≤Grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue through Day 21of the 28-day cycle

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** 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 adverse events 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

(for each cycle during induction and consolidation and maintenance)

Table 8.4

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Gastrointestinal disorders	Dyspepsia Grade 1-2	Dexamethasone	Treat with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	Gastric or duodenal ulcer Grade 1-2	Dexamethasone	Treat with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	Gastritis Grade 1-2	Dexamethasone	Treat with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	Dyspepsia ≥Grade 3	Dexamethasone	Omit dexamethasone until symptoms adequately controlled Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, discontinue dexa-methasone and do not resume Ixazomib and pomalidomide should be continued
	Gastric or duodenal ulcer ≥Grade 3	Dexamethasone	Omit dexamethasone until symptoms adequately controlled Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, discontinue dexa-methasone and do not resume Ixazomib and pomalidomide should be continued

Table 8.4			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
	Gastritis ≥Grade 3	Dexamethasone	Omit dexamethasone until symptoms adequately controlled Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole If symptoms persist despite above measures, discontinue dexa-methasone and do not resume 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 Ixazomib and pomalidomide should be continued
General disorders and administration site conditions	Edema (any location) ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)	Dexamethasone	Diuretics as needed, and decrease dexamethasone dose by 1 dose level If edema persists despite above measures, decrease dose another dose level Discontinue dexamethasone and do not resume if symptoms persist despite second reduction Ixazomib and pomalidomide should be continued
Psychiatric disorders	Delirium, delusion, depression, hallucination, euphoria ≥Grade 2	Dexamethasone	Omit dexamethasone until symptoms resolve Restart with one dose level reduction If symptoms persist despite above measures, discontinue dexamethasone and do not resume Ixazomib and pomalidomide should be continued

Table 8.4			
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**AGENT**	**ACTION****
Musculoskeletal and connective tissue disorders	Muscle weakness (any location) ≥ Grade 2 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 Discontinue dexamethasone and do not resume if symptoms continue to persist Ixazomib and pomalidomide should be continued
Metabolism and nutrition disorders	Hyperglycemia ≥ Grade 3 (>250 - 500 mg/dL; >13.9 - 27.8 mmol/L); hospitalization indicated	Dexamethasone	Treatment with insulin or oral hypoglycemics as needed If uncontrolled despite above measures, decrease dose by one dose level at a time until levels are satisfactory

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm

** 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 Full supportive care

Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

9.2 Steroid use

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

9.3 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

9.4 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.

9.5 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.

NOTE: Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study registration or drug dosing for any dosing day.

9.6 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.

9.7 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.

9.8 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

9.9a Prohibited medications

The following medications, medicinal products and procedures are prohibited during the study.

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 (If there were to be a drug-drug interaction with an inducer, MLN2238 exposure would be decreased):

- 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.

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 Pneumocystis jirovecii pneumonia [PJP (PCP)] prophylaxis

Since ixazomib is immunosuppressive and associated with an increased risk of PJP, all may receive prophylaxis during treatment. The choice of prophylactic medications will be left to the discretion of the treating physician. The decision to continue PJP prophylaxis beyond the time points noted is left to the discretion of the treating physician. Subjects who continue to demonstrate lymphopenia after the dosing of ixazomib has been discontinued should be considered for ongoing prophylaxis.

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

The site principal investigator is responsible for reporting any/all serious adverse events to the sponsor as described within the protocol, regardless of attribution to study agent or treatment procedure.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Summary of SAE Reporting for this study
(please read entire section for specific instructions):

WHO:	WHAT form:	WHERE to send:
All sites	Pregnancy Reporting http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	Mayo Sites – attach to MCCC Electronic SAE Reporting Form CancerCROSafetyIN@Mayo.edu
Mayo Clinic Sites	Mayo Clinic Cancer Center SAE Reporting Form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 AND attach MedWatch 3500A: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to [redacted]

Definitions

Adverse Event
Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected Adverse Reaction
Any adverse event for which there is a reasonable possibility that the drug caused the adverse event.

Expedited Reporting
Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest
Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

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 site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.

b. Determine whether the event is expected or unexpected (see Section 10.2).

c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

e. Determine if other reporting is required (see Section 10.5).

f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

NOTE: A severe AE is NOT the same as a serious AE, which is defined in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section

15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

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 or specificity, expedited reporting is required.

10.3 Attribution to agent(s) or procedure

When assessing whether an adverse event (AE) is related to a medical agent(s) medical or procedure, the following attribution categories are utilized:

Definite - The AE *is clearly related* to the agent(s)/procedure.
Probable - The AE *is likely related* to the agent(s)/procedure.
Possible - The AE *may be related* to the agent(s)/procedure.
Unlikely - The AE *is doubtfully related* to the agent(s)/procedure.
Unrelated - The AE *is clearly NOT related* to the agent(s)/procedure.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination) Arm

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.**

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for **investigational** agents/interventions.
- 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, unless hospitalization is required. Refer to Section 10.4 for specific AE reporting requirements or exceptions.

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 or specificity, expedited reporting is required.

- An increased incidence of an expected adverse event (AE) is based on the patients treated for this study at their site. A list of known/expected AEs is reported in the package insert or the literature, including AEs resulting from a drug overdose.
- Commercial agent expedited reports must be submitted to the FDA via MedWatch

3500A for Health Professionals (complete all three pages of the form).

http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

or

http://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/ListFormsAlphabetically/default.htm

Instructions for completing the MedWatch 3500A:
http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM387002.pdf

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6). *

Table 10.32

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

10.4 Expedited Reporting Requirements for IND Agents

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, 2]

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 to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥24 hrs	Not required	

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 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 1 and 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

NOTE: Refer to Section 10.32 for exceptions to Expedited Reporting

10.42 General Reporting instructions
The Mayo IND Coordinator will assist the sponsor-investigator in the processing of expedited adverse events and forwarding of suspected unexpected serious adverse reactions (SUSARs) to the FDA and IRB.

Use Mayo Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56 for investigational agents or commercial/investigational agents on the same arm.

Submit form MedWatch 3500A to the FDA, [redacted]

Send copies to:

Millennium Pharmacovigilance
Fax Number: [redacted]

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

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

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

Mayo Clinic Cancer Center (MCCC) Institutions:
If the event meets the criteria for IRB submission as a Reportable Event/UPIRTSO, provide the Reportable Event coversheet and appropriate documentation and use the Mayo Clinic Cancer Center Expedited Event Report form http://livecycle2.mayo.edu/workspace/?startEndpoint=MC4158-56/Processes/MC4158-56-Process.MC4158-56, to submit to CANCERCROSAFETYIN@mayo.edu. The Mayo Regulatory Affairs Office will review and process the submission to the Mayo Clinic IRB.

10.52 Death

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

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 (including 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.

10.53 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 will 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.

10.54 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 unless otherwise specified.

10.55 Pregnancy, Fetal Death, and Death Neonatal

If a female subject (or female partner of a male subject) taking investigational product becomes pregnant, the subject taking should notify the Investigator, and the pregnant female should be advised to call her healthcare provider immediately. The patient should have appropriate follow-up as deemed necessary by her physician. If the baby is born with a birth defect or anomaly, a second expedited report is required.

Prior to obtaining private information about a pregnant woman and her infant, the investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.551 Pregnancy

Pregnancy should be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions SOC. Pregnancy should be followed until the outcome is known.

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

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: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

Millennium Pharmacovigilance
Fax Number: [redacted]

10.552 Fetal Death

Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."

Any fetal death should be reported expeditiously, as **Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)"** under the Pregnancy, puerperium and perinatal conditions SOC.

10.553 Death Neonatal

Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration - Other (neonatal loss)"** under the General disorders and administration SOC.

10.6 Required routine reporting

10.61 Baseline and Adverse Events Evaluations

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

SYSTEM ORGAN CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
	White blood cell 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 maculo-papular	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X

10.62 All other AEs

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 10.6:

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)

10.6231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.6232 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.

10.7 Late Occurring Adverse Events

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).

10.8 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, Prashant Kapoor, 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 http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

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

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

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

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

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

SAE and Pregnancy Reporting Contact Information

Fax Number: [redacted]

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: [redacted]
- E-mail: [redacted]
- FAX: [redacted]
- Hours: Mon-Fri, 8 a.m. – 6 p.m. ET (US)

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

11.0 Treatment Evaluation

The International Myeloma Working Group (IMWG) uniform response criteria (Kumar et al, 2016) will be used to assess response to therapy.

11.1 Terms and definitions

- **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-protein 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 M-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, with the exception that quantitative IgG may not be used. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-protein 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.

- **Response terms:** The following response terms will be used: 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).

  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

NOTE: Quantitative IgG may not be used for defining measurable disease

  - Urine M-protein ≥200 mg/24 h

- Serum FLC assay: Involved FLC level ≥10 mg/dl provided serum FLC ratio is abnormal
- Bone marrow plasma cells ≥30%

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-protein) 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-protein, serum free light chain, or urine M-protein.
- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-protein or urine M-protein, but has had a detectable M-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 M-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 Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])

On Study Baseline Value	SPEP[4]	24 hr UPEP[2]	Ig FLC	BM Bx
Serum M-protein ≥1 g/dl, and urine M-protein≥200 mg/24 hrs	X	X		
Serum M-protein ≥ 1 g/dl, but urine M-protein <200 mg/24 hrs	X			
Serum M-protein <1 g/dl, and urine M-protein≥200 mg/24 hrs		X		
Serum M-protein < 1 g/dl, urine M-protein <200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X	
Serum M-protein <1 g/dl, urine M-protein<200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells				X[3]

[1] **SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy** 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] At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.

[4] If serum M-protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum M- protein, serum immunoglobulin free light chain (when primary determinant of response) and urine M- 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 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.

Table 11.5 Response and Progression	
IMWG MRD NEGATIVITY CATEGORY	**RESPONSE CRITERIA [a]**
Sustained MRD	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)
Flow MRD [k]	Absence of phenotypically aberrant clonal plasma cells by NGF on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD [k]	Absence of clonal plasma cells by NGS on bone marrow aspirates in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Imaging Plus MRD [k]	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less than mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue
STANDARD IMWG RESPONSE CATEGORY	**RESPONSE CRITERIA [a]**
Stringent Complete Response (sCR) [b]	• CR as defined *plus* • Normal FLC ratio *and* • Absence of clonal PCs by immunohistochemistry or 2- to 4-color flow cytometry [i]
Complete Response (CR) [b, l]	• Negative immunofixation of serum and urine [c] *and* • Disappearance of any soft tissue plasmacytoma *and* • <5% PCs in Bone Marrow *and* • If the only measurable disease is FLC, a normal FLC ratio [d]
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis [c] *or* • ≥90% reduction in serum M-protein and urine M-protein <100 mg/24 h [c] • If the only measurable disease is FLC, a >90% reduction in the difference between involved and uninvolved FLC levels
Partial Response (PR)	• If present at baseline, ≥ 50% reduction of serum M-protein and reduction in 24-hour urinary M-protein by ≥90% or to <200 mg/24hrs [c] • If the only measurable disease is FLC, a ≥50% reduction in the difference between involved and uninvolved FLC levels • If the only measurable disease is BM, a ≥ 50% reduction in BM PCs (provided the baseline PCs was ≥ 30%) • If present at baseline, ≥ 50% reduction in the size (SPD) of soft tissue plasmacytomas [j]
Minor Response (MR)	• If present at baseline, ≥25% but ≤ 49% reduction of serum M

Table 11.5 Response and Progression	
	protein *and* reduction in 24-hour urine M-protein by 50-89% which still exceeds 200mg/24 hours [c] *and* • If present at baseline, ≥50% reduction in the size (SPD) of soft tissue plasmacytoma [j]
Stable Disease (SD)	• Not meeting criteria for sCR, CR, VGPR, PR, MR or PD
Progressive Disease (PD) [b, h]	Increase of 25% from lowest value in any of the following [f, g]: • Serum M-protein (absolute increase must be ≥ 0.5 g/dL) *and/or* • Urine M-protein (absolute increase must be ≥ 200 mg/24 hrs) *and/or* • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) *and/or* • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be ≥ 10%) [e] Or any one or more of the following: • Development of new bone lesion or soft tissue plasmacytoma or ≥50% increase from nadir in the size (SPD) of existing bone lesions or soft tissue plasmacytoma or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis [j] • 50% increase in circulating plasma cells (minimum of 200 cells per L) if this is the only measure of disease
Clinical Relapse	One or more of the following direct indicators of increasing disease and/or end-organ dysfunction that are considered related to the underlying plasma cell proliferative disorder: 1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, magnetic resonance imaging, or other imaging 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dL; >2.875mM/L) 4. Decrease in hemoglobin of more than 2 g/dL (1.25mM) or to less than 10 g/dL 5. Rise in serum creatinine by more than or equal to 2 mg/dL (≥177mM/L) 6. Hyperviscosity

[a] All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy. MRD tests should be initiated only at the time of suspected complete response. sCR, CR, VGPR, PR, MR and SD categories and MRD require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported. 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. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

[b] CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

[c] If more than one M protein spike meets the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

[d] In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

[e] Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC

[f] A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-protein is ≥5 g/dL, an increase in serum M-protein of ≥1 g/dL is sufficient to define disease progression.

[g] 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.

[h] Progressive disease should be confirmed on two consecutive evaluations, where the timing of confirmation is per the treating physician and can be done immediately within the same cycle or on the next cycle. 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.

[i] Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

[j] Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).

[k] Requires a complete response as defined in table 11.5. MRD tests should be initiated only at the time of suspected complete response. MRD requires no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

11.6 Criteria for engraftment (for hematopoietic stem cell transplant studies only)

Engraftment is defined as:

- The first day of three consecutive days on which the absolute neutrophil count (ANC) >500/mm^3

and

- The first of three consecutive days with an untransfused platelet count >20,000/mm^3.

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. Distinguish between SPEP measurements vs. quantitative IgA measurement vs. quantitative IgD or IgM measurement for serum M-spike

12.2 Number of prior therapies: 1-3 vs. 4 or more

12.3 Revised international staging system (R-ISS): Stage I vs. Stage II vs. Stage III

Risk Factors	Serum β2 microglobulin	Serum albumin	Del(17p) and/or t(4;14) and/or t(14;16)	Abnormal LDH level
Stage I (Criteria in all columns must be met)	<3.5 mg/L	≥3.5 g/dL	No	No
Stage II	All other possible combinations (not Stage I or Stage III)			
Stage III (Criteria in all columns must be met)	>5.5 mg/L	NA	At least one = Yes	

12.4 Extramedullary disease at the time of study entry: Yes vs. no

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are MRD negative, 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 off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly 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 End of Active Treatment/Cancel Notification 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. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Event monitoring will be required per Section 18.0 of the protocol.

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 End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected under IRB #521-93

Note: Research blood and bone marrow collection per protocol IRB 521-93 will be done after consenting for 521-93 and according to that protocol. All processing will be done on Stabile 6.

Correlative Study (Section 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)	End of Cycle 4 (post Induction/ Pre ASCT	~Day 100 post ACST	Post consolidation	Ongoing Maintenance After 1 year from initiation of maintenance
Minimal residual disease by Flow cytometry	Mandatory In patients who have achieved at least CR	Bone marrow aspirate	ACD (yellow)	6 mL (1)	X	X	X	X

14.2 Collection and Processing

14.21 Flow cytometry: This will be performed on bone marrow aspirate following a wash no lyse method on fresh samples.

14.3 Background and Methodology

14.3 1 Minimal residual disease evaluation: Currently 30-40% of patients achieve a CR with initial therapy. In most cases, patients classified as CR in reality have minimal residual disease (MRD) since (i) many such patients relapse, and (ii) residual clonal disease is detectable in most by more sensitive techniques such as multiparameter flow cytometry and PCR based techniques.(Sarasquete, Garcia-Sanz et al. 2005; Mateo, Montalban et al. 2008; Paiva, Vidriales et al. 2009). We will determine minimal residual disease positivity at various stages of treatment, among patients achieving a conventional complete response. Bone marrow aspirates will be evaluated for presence of clonal plasma cells a well as the ratio of clonal to non-clonal plasma cells after 4 cycles and whenever a CR is suspected and a marrow is done.

MRD detection will be done on BM samples as previously described32. Plasma cells are identified by their characteristic CD45/CD38/CD138 staining pattern with light chain restriction and CD19/CD56 phenotype on each case. One ml (milliliter) of BM (bone marrow) is subjected to flow cytometry on a Cantos Flow Cytometer. Samples are collected ungated, up to one million events per tube.

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 (MLN9708) 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.

15.13 **Preparation and storage**: Ixazomib capsules (0.2 mg, 0.5 mg, 2.0 mg), individually packaged in blisters, can be stored at 2ºC to 8ºC or “Do not store above 25°C. Do not freeze." Ixazomib capsules (2.3 mg, 3.0 mg, 4.0 mg, and 5.5 mg), individually packaged in blisters can be stored at “2°C - 8°C” or “Do not store above 30°C. 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 units that comprise 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. Any extremes in temperature should be reported as an excursion and will be managed on a case by case basis. 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 (PK) 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 C_{max} and $AUC_{0\text{-last}}$ were reduced in the presence of rifampin by approximately 54% and 74%, respectively. As a result, the coadministration of strong CYP3A inducers with ixazomib should be avoided. 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 LenDex 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, 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, papular 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 reactions, 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 Takeda Pharmaceuticals, Inc.

15.19 Nursing guidelines

15.191 Capsules must be administered intact and should not be opened or manipulated in any way. Additionally, capsules should remain in the blister packs until they are ready to be taken.

15.192 Capsules should be taken on an empty stomach (either 1 hours before or 2 hours after meals) with 8 oz of water.

15.193 Cytopenias have been observed. Monitor CBC w/diff. Instruct patient to report any signs or symptoms of infection or bleeding to the study team.

15.194 GI side effects have been seen (nausea, diarrhea, vomiting), treat symptomatically and monitor for effectiveness of intervention.

15.195 Rash has been seen. Rarely Steven Johnson syndrome (SJS) has been seen with this agent. Instruct patients to report any rash to study team.

15.196 Assess patients concomitant medications, including over the counter and supplements. MLN9708 is metabolized through both CYP and non-CYP enzymes, and drug to drug interactions exist. Instruct patients not to start

any new medications or supplements without checking with the study team first.

15.197 Fatigue has been seen. Instruct patient in energy conserving lifestyle.

15.198 Insomnia can be seen. Treat symptomatically and monitor for effectiveness.

15.199a Patients who have had an allergic reaction to boron or boron containing products should not take MLN9708.

15.199b The following rare but life threatening conditions have been seen with agent: CHF, liver failure, TTP, TLS, renal failure, bowel obstruction, and RPLS, transverse myelitis, progressive multifocal leukoencephalopathy. Monitor labs closely, instruct patient to report any new or worsening symptoms to the study team and provide further assessment based on symptoms.

15.2 Pomalidomide (Pomalyst®)

15.21 **Background**: Pomalidomide 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 polyubiquitination 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 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 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 month of therapy may be dispensed.

15.24 **Administration:** Pomalidomide is administered by mouth at approximately the same time each day. 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 C_{max} 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 half-life ($t_{1/2}$) of pomalidomide was approximately 7.5 hours.

In pomalidomide renal studies, no dose adjustment was required for subjects with renal impairment. On hemodialysis days, subjects were instructed to take pomalidomide following hemodialysis. No dose adjustment of pomalidomide is required for patients with hepatic impairment as defined by the Child-Pugh criteria.

15.26 **Potential Drug Interactions**: Pomalidomide is partially metabolized by CYP1A2 and CYP3A4/5. 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 known potential toxicities, ≥0.1% - <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, dysesthesia, 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 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.

15.29 Nursing Guidelines

15.291 Agent is known to be teratogenic in rabbits. Therefore all women who are pregnant or who could become pregnant, should not handle the agent outside of the original packaging. Chemotherapy gloves should be worn if contact is necessary.

15.292 Because of the similarity of this agent to thalidomide certain precautions MUST be employed by all subjects on protocol and for 4 weeks after discontinuation of agent. Instruct patients the following must be adhered to: No donation of tissue/blood/semen/sperm; sexually active males/ females must use protocol-specific contraception (regardless of fertility status-i.e. history of vasectomy).

15.293 Cytopenias are common (neutropenia most common). Monitor CBC closely and instruct patient to report any signs/symptoms of infection or unusual bruising or bleeding to the study team.

15.294 Thrombotic events have been reported. Anticoagulation prophylaxis may be recommended. Instruct patients to report any problems with bleeding, extremity pain or swelling, or shortness of breath to the study team immediately.

15.295 Patients may experience cough, URI, pneumonia, or sinusitis. Instruct patients to report respiratory symptoms to the study team.

15.296 Gastrointestinal side effects consisting of diarrhea, constipation, stomatitis, nausea, decreased appetite, and abdominal pain have been seen. Treat symptomatically and monitor for effectiveness.

15.297 Drug should be taken without food (at least 2 hours before or 2 hours after a meal). Do not open or crush capsules.

15.298 Patients may experience myalgias and muscle spasms. Treat symptomatically and monitor for effectiveness.

15.299a Fatigue is common. Instruct patient in energy conserving lifestyle.

15.299b Warn patients about the possibility of peripheral neuropathy, headache, confusion, and dizziness.

15.299c Patients may experience URI, pneumonia, dyspnea, and cough. Instruct patients to report respiratory symptoms to the study team.

15.299d Severe dermatologic reactions have been seen (including urticaria). Instruct patient to report and rash or skin changes to the study team.

15.299e All patients must be registered in the POMALYST REMS program. See protocol for more details.

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.

15.39 Nursing Guidelines:

15.391 Monitor patient regularly for hypertension, CHF and other evidence of fluid retention.

15.392 Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.

15.393 Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.

15.394 Evaluate signs of infection, particularly local candidal infections and treat appropriately**.**

15.395 Monitor blood glucose frequently.

15.396 Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

15.397 Advise patient that easy bruising is a side effect.

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a phase II study of a novel regimen of ixazomib in combination with pomalidomide and dexamethasone for treatment of patients who are being considered for single ASCT for relapsed or refractory multiple myeloma. The study is designed to assess the progression-free survival at 18 months (PFS18) using a one-stage binomial study design.

16.11 Primary Endpoint

The primary endpoint of this trial is the proportion of patients alive and free from disease progression at 18 months from study entry. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment, will be evaluable for progression-free survival at 18 months (PFS18), unless they are determined to be a major violation.

16.2 Statistical Design:

16.21 Decision Rule

In a previous study including 112 patients who received a delayed autologous transplant after IMiD-based initial therapy, median progression-free survival from the time of transplant was 15.9 months (Kumar S 2012). In two additional studies with 64 patients and 65 patients who received novel agents during the pre-ASCT induction, the median progression-free survival from time of transplant was 22.2 months and 18 months, respectively, in patients who received a delayed transplant (Dunavin NC, 2013; Remenyi P, 2016).

Patients on the proposed study will also be undergoing delayed autologous transplantation; however, progression-free survival will be measured from study entry. Based on previous studies, a PFS18 rate from time of study entry of 50% would not be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 50%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 75%. The following one-stage binomial design uses 21 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 50%.

16.212 Final Decision Rule: If 13 or fewer successes are observed in the first 21 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 14, 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.

16.22 Sample Size

The one stage study design to be used is fully described above. A maximum of 21 evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. We anticipate accruing an additional 4 patients to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the total sample size will be 25 patients.

16.23 Accrual Rate and Study Duration

We anticipate accruing 2 patients per month to this study, and hence the enrollment period will be approximately 2 years. An individual patient is expected to complete induction, ASCT and consolidation phases within 15 months of enrollment, after which ixazomib maintenance phase will start in which the drug is given until progression or unacceptable toxicity. The minimum duration before results may be reported is expected to be approximately 3.5 years, or until the last patient accrued has been observed for at least 18 months.

16.24 Power and Significance Level

Assuming that the number of successes is binomially distributed, the significance level is 0.095. The probability of declaring that this regimen warrants further studies (i.e. statistical power) 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...	0.50	0.55	0.60	0.65	0.70	0.75
Then the probability of declaring that the regimen warrants further study is…	0.095	0.197	0.350	0.537	0.723	0.870

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 18 months.

16.31 Primary Outcome Analyses:

16.311 Definition: The primary endpoint of this trial is the proportion of patients alive and free from disease progression at 18 months from study entry. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment, will be evaluable for progression-free survival at 18 months unless they are determined to be a major violation. *Definition of Success*: An evaluable patient will be classified as a

treatment success for the primary endpoint if they are alive and free from disease progression at 18 months from registration.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportion will be calculated. If patients are censored prior to 18 months post registration (which is unlikely given our data from past trials in a similar patient population), a Kaplan Meier (Kaplan, E. and Meier, P., 1958) estimate for PFS18 along with the 95% confidence intervals will be reported. We recognize that applying this approach will, however, reduce the stated statistical power of our primary analysis.

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 The overall response rate will be estimated by the number of patients who achieve a sCR, CR,VGPR, or PR divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true overall response rate will be calculated.

16.322 The ≥VGPR response rate will be estimated by the number of patients who achieve a sCR, CR, or VGPR divided by the total number of evaluable patients. All evaluable patients will be used for this analysis. Exact binomial 95% confidence intervals for the true overall ≥VGPR response rate will be calculated.

16.323 Overall survival is defined as the time from registration to the last date of documentation of follow-up or death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier (Kaplan, E. and Meier, P., 1958)

16.322 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 in CR at various stages of treatment: after induction, day # 100 after SCT, after consolidation and during maintenance at one year from initiation of maintenance therapy. 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.

16.324 Engraftment kinetics (WBC and platelet) following single salvage ASCT for relapsed disease will be measured by assessing the timing of recovery of bone marrow function. Neutrophil engraftment will be defined as the first of the three days of neutrophil count above 500/microliter and platelet engraftment as the first day of >20,000 platelets/microliter, untransfused.. The median time to engraftment of neutrophil count and platelet count from the day of infusion of autologous stem cells (day 0) will be summarized using descriptive statistics.

16.4 Data & Safety Monitoring

16.41 Reviews

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.

16.42 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 3 or more patients in the first 10 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.
- if after the first 10 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.

16.5 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 3.5 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 18 months.

16.6 Inclusion of Women and Minorities

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

16.62 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.

16.63 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	8	16	0	24
Ethnic Category: Total of all subjects*	8	17	0	**25**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	0	1	0	1
Native Hawaiian or other Pacific Islander	0	0	0	0
White	8	16	0	24
Racial Category: Total of all subjects*	8	17	0	**25**

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 Data Submission Schedule.

18.2 Event monitoring

See Section 4.2 and data submission table for the event monitoring schedule.

18.3 CRF completion

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 pro gression 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 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.

18.7 Incomplete materials

Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing

information is received. A list of the missing documents will be made available to the appropriate co-sponsor/participant.

18.8 Overdue lists

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 co-sponsor/participant. The query will be sent to the appropriate co-sponsor/participant who will make the correction and return the query and documentation of correction back to the QAS.

19.0 Budget

19.1 Costs charged to patient: Routine clinical care

19.2 Tests to be research funded: Research testing on bone marrow specimens (per IRB #521-93).

19.3 Other budget concerns: Ixazomib to be provided to the patient by Takeda free of charge.

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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 http://www.ecog.org/general/perf_stat.html

Appendix II Patient Medication Diary

Name _____ **Study ID** _____

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: _____

Study Coordinator Use Only

Number of pills returned _____ Number of vials returned: _____

Discrepancy Yes____/No____ Verified by _____ Date_____

Maintenance Diary for Ixazomib Only

Name_____ **Study ID**_____

Please complete this diary on a daily basis. Write in the amount of the dose of ixazomib 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 ixazomib, please record this information.

Week of: _____

Study Drug	***Day 1***	***Day 2***	***Day 3***	***Day 4***	***Day 5***	***Day 6***	***Day 7***
Ixazomib							

Week of: _____

Study Drug	***Day 8***	***Day 9***	***Day 10***	***Day 11***	***Day 12***	***Day 13***	***Day 14***
Ixazomib							

Week of: _____

Study Drug	***Day 15***	***Day 16***	***Day 17***	***Day 18***	***Day 19***	***Day 20***	***Day 21***
Ixazomib							

Week of: _____

Study Drug	***Day 22***	***Day 23***	***Day 24***	***Day 25***	***Day 26***	***Day 27***	***Day 28***
Ixazomib							

Patient Signature: _____

My next scheduled visit is: _____

If you have any questions, please call: _____

Study Coordinator Use Only

Number of pills returned Number of vials returned:

Discrepancy Yes____/No____ Verified by _____ Date_____