Mayo Clinic Cancer Center

Phase 2 Trial of Pembrolizumab, Ixazomib and Dexamethasone for Relapsed Multiple Myeloma

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Drug Availability
Commercial Agent: Dexamethasone
Drug Company Supplied agents: Ixazomib (Takeda), Pembrolizumab (Merck) (IND# 136950)

Merck # 54330
Takeda # X16105

√Study contributor(s) not responsible for patient care

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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]
Drug administration, infusion pumps, nursing guidelines	[redacted]
Forms completion and submission	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Serious Adverse Events	[redacted]

*No waivers of eligibility per NCI

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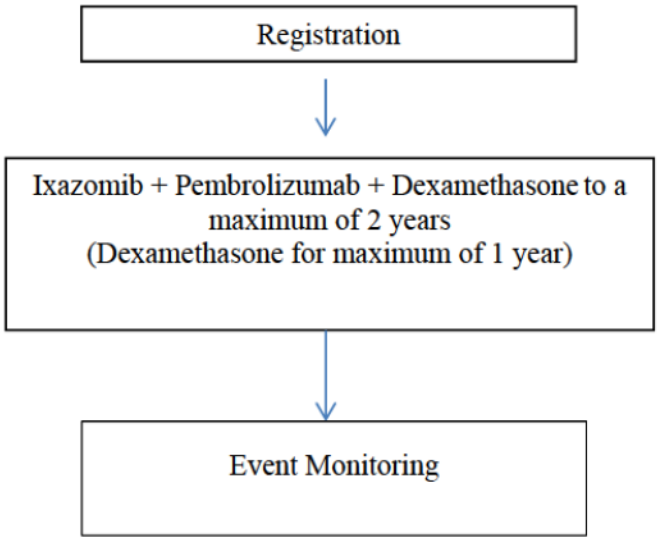
Schema



PD at any time
Unacceptable adverse events → **Event Monitoring**
Patient refusal
Subsequent treatment for myeloma

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

Cycle length = 84 days

Patients are allowed to collect stem cells after 1 cycle of initial therapy. Stem cells can be collected using standard institutional protocols. Any delay beyond 4 weeks should be discussed with the study PI prior to reinitiating protocol therapy.

Generic name: Ixazomib Brand name(s): Ninlaro® Mayo Abbreviation: MLN9708 Availability: Provided by Takeda	Generic name: Dexamethasone Brand name(s): Decadron® Mayo Abbreviation: DXM Availability: Commercial	Generic name: Pembrolizumab Brand name(s): Keytruda® Mayo Abbreviation: MK-3475 Availability: Provided by Merck

1.0 Background

1.1 Multiple Myeloma

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

1.2 Ixazomib:

Ixazomib, which has been formulated for both intravenous (IV) and oral (PO) administration, is a small molecule proteasome inhibitor. Ixazomib citrate (MLN9708) is the citrate ester of the biologically active boronic acid form, ixazomib MLN2238, which is structurally similar to bortezomib. In water or aqueous systems, ixazomib citrate rapidly hydrolyzes to MLN2238, therefore all doses and concentrations are expressed as MLN2238. Nonclinical studies were conducted with a solution of either MLN2238 or MLN2238 in equilibrium with ixazomib citrate. Similar to bortezomib, MLN2238 potently, reversibly, and selectively inhibits the 20S proteasome. However, in contrast to bortezomib, it has a shorter dissociation half-life ($t_{1/2}$) 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.

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

In Vitro Pharmacology: 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 C_{max} 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. At higher than clinical concentrations, ixazomib was metabolized by multiple CYP isoforms with estimated relative contributions of 3A4 (42%), 1A2 (26%), 2B6 (16%), 2C8 (6%), 2D6 (5%), 2C19 (5%) and 2C9 (<1%). MLN2238 is neither an inhibitor of CYP isozymes 1A2, 2C9, 2C19, 2D6, or 3A4 (IC50 >30 μM, with an estimated inhibition dissociation constant [Ki] >15 μM) 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.

See the IB for further details.

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 C_{max} 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 C_{max} 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.

Toxicology: All studies discussed in this section were conducted with a solution of either MLN2238 or MLN2238 in equilibrium with ixazomib citrate. Because ixazomib citrate 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, for which ixazomib is the next-generation molecule. MLN2238 did not cause significant toxicities that have not been previously observed after dosing with bortezomib. Therefore, on the basis of the similarity in the toxicity profile in rats between MLN22338 and bortezomib, MLN2238 is not known to present any additional safety risks beyond those that occur after treatment with bortezomib. In addition, there were no significant findings at tolerated exposures in dogs observed after PO administration that were not seen after IV administration, and similar exposures were tolerated regardless of the route of administration.

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

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

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

Further details are presented in the IB.

1.3 Clinical Experience with Ixazomib

Ixazomib has been studied in several phase 1 and phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. Ixazomib is available as an intravenous and oral formulation. Regardless of the route of administration in the twice-weekly dosing schedule, ixazomib is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral ixazomib has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a different yet related plasma cell dyscrasia, systemic light chain (AL) amyloidosis. Details of these trials can be found in ClinicalTrials.gov and the ixazomib IB.

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 (t1/2) 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 Cmax and AUC0-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 AUC0-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 m2), 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.

1.4 Overview of the Oral Formulation of ixazomib

The safety profile indicates that oral ixazomib is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care. From experience from phase 1 through 3 studies the major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 24 months.

Relapsed MM: Single-agent, Weekly ixazomib (Study C16004):
Study C16004 is an open-label, dose-escalation, phase 1 study of ixazomib administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. In this study, 2 of 3 patients experienced protocol-defined DLTs (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m^2. As per protocol, subsequent patients were treated at 1 dose level below (2.97mg/m^2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral ixazomib was determined to be 2.97 mg/m^2.

Once the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled in order to further evaluate the safety, tolerability, efficacy, PK, and pharmacodynamics of oral ixazomib and included:

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];
2. Carfilzomib expansion cohort
3. Proteasome Inhibitor-Naïve expansion cohort
4. VELCADE-Relapsed expansion cohort

Sixty patients with relapsed and/or refractory multiple myeloma were enrolled. The MTD was determined to be 2.97 mg/m^2. Dose-limiting toxicities were grade 3 nausea, vomiting, and diarrhea in 2 patients, and grade 3 skin rash in 1 patient. Common drug-related adverse events were thrombocytopenia (43%), diarrhea (38%), nausea (38%), fatigue (37%), and vomiting (35%). The observed rate of peripheral neuropathy was 20%, with only 1 grade 3 event reported. Nine (18%) patients achieved a partial response or better, including 8 of 30 (27%) evaluable patients treated at the MTD. Pharmacokinetic studies suggested a long terminal half-life of 3.6 to 11.3 days, supporting once-weekly dosing.

Newly Diagnosed Multiple Myeloma (C16005):
In Study C16005, ixazomib is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle.[13] Patients with newly diagnosed MM were enrolled and treated with oral ixazomib (days 1, 8, and 15) plus lenalidomide 25 mg (days 1-21) and dexamethasone 40 mg (days 1, 8, 15, 22) for up to twelve 28-day cycles, then maintenance therapy with ixazomib (same schedule) every 28 days until progression. Patients were allowed to undergo stem cell collection after 3 cycles and discontinue for autologous stem cell transplant (ASCT)

after 6 cycles. Overall, 65 patients were enrolled, 15 in Phase 1 and 50 in Phase 2. Patients received a median of 6 cycles (range 1-19) with 27 (42%) remaining on treatment as of November 2012. Of those who have undergone stem cell mobilization, a median yield was 11.3 x 10^6 CD34+ cells/Kg (range 5-28). Ixazomib MTD was established as 2.97 mg/m^2 and RP2D was selected as 2.23 mg/m^2; RP2D translates to a 4 mg fixed dose based on population PK results. Among the 64 evaluable patients, the overall response rate was 92%, including 55% VGPR and 23% CR. Median time to first response was 0.92 months (range 0.89-6.44).

Relapsed Multiple Myeloma (Tourmaline MM01): This international phase 3 trial enrolled adults with RRMM who had received 1–3 prior lines of therapy and who were not refractory to prior lenalidomide or PI-based therapy. Patients were randomized 1:1 to receive ixazomib 4 mg or matching placebo weekly on d 1, 8, and 15, plus lenalidomide 25 mg PO on d 1–21 and dexamethasone 40 mg PO on d 1, 8, 15, and 22, in 28-day cycles. 722 patients were randomized (360 IRd; 362 Rd); 19% had high-risk cytogenetics by FISH (del(17), t(4;14), or t(14;16)), including 10% del(17). The study demonstrated significantly better PFS with IRd (20.6 months) compared with Rd (14.7 months); a 35% improvement in PFS (HR 0.742; p=0.012). The PFS improvement was seen in all patient subgroups, especially in patients with del17p, where the improvement with the combination was quite striking.

Potential Risks and Benefits of ixazomib:

Please refer to the current ixazomib Investigator's Brochure (IB).

1.5 Pembrolizumab:

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been

shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda® (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 –

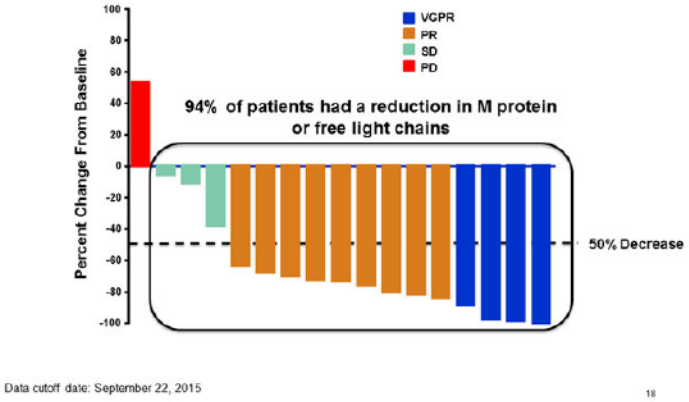
5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Pembrolizumab experience in multiple myeloma: The keynote-23 trial enrolled patients with RRMM who have failed ≥2 prior therapies including a proteasome inhibitor and an IMiD. During the dose determination phase, cohorts of 3-6 patients were enrolled at 2 mg/kg of pembrolizumab every 2 weeks (Q2W) in combination with 10 mg or 25 mg of lenalidomide on days 1-21 and 40 mg low-dose dexamethasone weekly, to be repeated every 28 days. After an MTD was identified, additional patients were enrolled at a fixed dose of 200 mg of pembrolizumab in combination with lenalidomide and dexamethasone. Overall, 51 patients with a median of 4 prior lines of therapy were enrolled, 78% of who were refractory to the last line of therapy. Most common AEs noted included cytopenias, fatigue and gastrointestinal side effects. DLTs seen included tumor lysis, neutropenia and pneumonia. Overall response rate was 50% including 16% with VGPR or better; the corresponding numbers were 38% and 13% among the patients who were refractory to lenalidomide.



In a similar phase II study, 24 patients with RRMM received 28-day cycles of pembrolizumab (at a dose of 200 mg IV) every 2 weeks (in a run off phase, first 6 patients received 200 mg IV every 4 weeks) plus pomalidomide (4 mg daily x 21 days) and dexamethasone 40 mg weekly. Patients with relapsed and/or refractory myeloma with two or more lines of prior therapy that included an IMid and a proteasome inhibitor were eligible for this trial. Thirty-three patients, most refractory to proteasome inhibitors and IMiDs (70% double refractory), were enrolled. The overall response rate was 60% among the 27 patients evaluable for response, including 5 patients with a VGPR or better.

1.6 Rationale for the current trial:

Currently, there is considerable amount of work is being done to enhance this regimen. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Up regulation of PD-1 ligands occur in some tumors and signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. In the setting of myeloma, B-cell responses are altered to a state of functional hypogammaglobulinemia, leading to an increased risk for infections. T-cell-mediated immunity is also severely impaired in MM with T-helper (Th)1/Th2 imbalance leading to immune dysfunction. Several studies have shown that PD-L1 is absent from normal plasma cells, whereas it is expressed on myeloma cell lines and primary myeloma tumor cells from patients with MM. It has been demonstrated that PD-1 expression is up regulated on T cells isolated from patients with MM, suggesting that this pathway is of importance in mediating the immunosuppressive state in this patient population. Benson et al. have shown that NK cells from MM patients express PD-1 and suggested that PD-1/PD-L1 interactions undermine the immunological control of MM by NK cells. They have also demonstrated that the application of an anti-PD-1 monoclonal antibody enhances the cytolytic activity of NK cells against autologous, primary MM cells. Preliminary results from ongoing trials of pembrolizumab with lenalidomide or pomalidomide have demonstrated evidence of activity. Ixazomib has excellent activity in MM, and proteasome inhibitors have been shown to be active in combination with other immunotherapy approaches such as elotuzumab and daratumumab. Given these findings, it is rational to evaluate the combination of pembrolizumab in combination with ixazomib and dexamethasone in relapsed myeloma.

2.0 Goals

2.1 Primary

To determine the overall response rate (>=PR) of pembrolizumab in combination with standard doses of ixazomib and dexamethasone, in patients with relapsed symptomatic MM.

2.2 Secondary

2.21 To determine the ≥ very good partial response (VGPR) and complete response (CR) rate of pembrolizumab added to standard doses of ixazomib and dexamethasone in relapsed myeloma.

2.22 To determine the progression free survival and overall survival among patients with relapsed MM following treatment with the combination of pembrolizumab, ixazomib and dexamethasone.

2.23 To determine the toxicities associated with pembrolizumab added to standard doses of ixazomib and dexamethasone in patients with relapsed MM.

2.3 Correlative Research

2.31 PDL-1 expression on myeloma cells and non-tumor cell compartments from the bone marrow will be assessed at baseline

2.32 Measures of T-cell activation / exhaustion will be assessed at baseline and after Cycle 1 and Cycle 3.

2.33 NK cell function and numbers will be evaluated at baseline and after Cycle 1 and Cycle 3.

3.0 Patient Eligibility

3.1 Inclusion Criteria

3.11 Diagnosis of relapsed, symptomatic multiple myeloma by IMWG diagnostic criteria for multiple myeloma.

3.12 Age ≥18 years

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 ≥75000/mm^3 Note: Platelet transfusion is not allowed ≤3 days prior to registration.
- Hemoglobin ≥8.0 g/dL
- Total bilirubin ≤ 1.5 x ULN
- ALT and AST ≤ 2.5 x ULN

*Cockcroft-Gault Equation:

Creatinine clearance for males = (140 - age)(actual body weight in kg)
(72)(serum creatinine in mg/dL)

Creatinine clearance for females = (140 - age)(actual body weight in kg)(0.85)
(72)(serum creatinine in mg/dL)

3.14 Must have relapsed or refractory disease after treatments including three therapies: proteasome inhibitors, IMiDS, and anti-CD38 antibody.

3.15 Measurable disease of multiple myeloma as defined by at least ONE of the following:

- Serum monoclonal protein ≥1.0 g/dL (see Section 11.1 for definition)
- ≥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.

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

3.17 Provide informed written consent.

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

3.19a Willing to follow strict birth control measures as detailed in Section 9.9i.

Female patients: If they are 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 120 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 [eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

Male patients: 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 120 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
- Agre e to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

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

3.19c Willing to provide bone marrow and blood samples for planned research (see Sec. 14.1).

3.2 Exclusion Criteria

3.21 Myeloma disease that is refractory to ixazomib treatment.

3.22 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include early stage cancers (carcinoma in situ or Stage 1) treated with curative intent, basal cell carcinoma of the skin, squamous cell

carcinoma of the skin, in situ cervical cancer, or in situ breast cancer that has undergone potentially curative therapy.

3.23 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 women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

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

3.25 Other concurrent chemotherapy, or any ancillary therapy considered Investigational ≤14 days prior to study registration.
NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.

3.26 Peripheral neuropathy ≥Grade 3 on clinical examination or Grade 2 with pain during the screening period.

3.27 Major surgery ≤14 days prior to study registration.

3.28 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 study drugs

3.29a Participation in any other clinical trials with other investigational agents not included in this trial ≤21 days prior to registration.

3.29b Has active autoimmune disease that has required systemic treatment ≤2 years prior to study registration (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs).
NOTE: Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.29c Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.

3.29d Has a known history of interstitial lung disease.

3.29e Has an active infection requiring systemic therapy.

3.29f Has a history of current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.29g Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

3.29h Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

3.29i Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

3.29j Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.29k Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.29l Has a known history of active TB (Bacillus Tuberculosis)

3.29m Has received a live vaccine ≤30 days prior to study registration.

3.29n Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis.

3.29o Allogeneic hematopoietic stem cell transplant.

3.29p Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort ≤14 days prior to registration.

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

4.0 Test Schedule

4.1 Schedule of assessments

Tests and Procedures	*Days Prior to Registration*		*Weekly (for first cycle)*[1]	*Every cycle*		*End of treatment*
	≤30 days	*≤14 days*		*Day 1, Pre-treatment* (±4 days)	*Day 22, 43, 64 Pre-treatment* (±1 day)	
Complete medical history	X					
Adverse Event monitoring		X		X	X	X
Physical exam, including weight and vital signs		X		X	X[11]	X
Height		X				
Performance status (ECOG scale)		X		X		X
CBC with diff.		X	X	X[10]	X	X
Prothrombin time (PT)	X					
Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; Total and Direct bilirubin; SGOT (AST); SGPT (ALT), serum creatinine, calcium		X	X	X[10]	X	X
Thyroid function cascade (TSH, T3, T4, TPO antibody)	X			X	X	
LDH, $Beta_2$-microglobulin, C-reactive protein, Plasma cell assessment	X					
Electrophoresis of serum and urine		X		X[13]	X[13]	X
Affected Immunoglobulin		X		X[7]	X[7]	X[7]
Immunofixation serum and urine	X			X[2]	X[2]	X[2]
Immunoglobulin free light chain		X		X[4]	X[4]	X[4]
X-ray skeletal survey or low dose whole body CT	X					
Bone marrow aspirate and biopsy[9]	X			X[5]	X[5]	X[5]
Research bone marrow [R]				X[5]	X[5]	X[5]
Research blood sample [R]				X[8]	X[8]	X[8]
Chest x-ray	X					
PET CT[12]				X[12]		
Pregnancy test[3]		X[3]				

Tests and Procedures	*Days Prior to Registration*			*Every cycle*		
	≤30 days	*≤14 days*	*Weekly (for first cycle)*[1]	*Day 1, Pre-treatment* (±4 days)	*Day 22, 43, 64 Pre-treatment* (±1 day)	*End of treatment*
Patient Medication Diary (Appendix II)[6]				X		X

1) All scheduled visits will have a window of ±4 days unless otherwise stated
2) Immunofixation (IF) needed only in the absence of M-spike to document CR or sCR.
3) For persons of childbearing potential only. Must be done ≤7 days prior to registration and ≤72 hours prior to receiving the first dose of study drug. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
4) FLC is required only if used to assess disease response during active phase
5) Collected prior to C1D1 treatment; at the end of 2 cycles, and to document progression or CR at any time point.
6) The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution.
7) Affected immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, IgD, or IgM . Not applicable if patient "non-secretory" or if patient has no heavy chain, i.e. light chain myeloma.
8) Collected prior to C1D1 and C1D22; then evey cycle prior to D1 treatment; and to document progression or CR at any timepoint.
9) The following testing may be done if clinically indicated: Myeloma FISH, plasma cell proliferation, and flow cytometry (MRD)
10) Does not need to be repeated at Cycle 1 Day 1. Baseline values can be used for Cycle 1.
11) If patient is stable after 2 cycles, physical exam can be decreased to Weeks 1 and 7 of each cycle.
12) Only if clinically indicated for MRD negative patients every 12 weeks.
13) Urine Electrophoresis required only if used to assess disease response.

R) Research funded (see Section 19.0). Will be charged to study and not to patient's account.

4.2 Event Monitoring/Survival Follow-up

	Event Monitoring Phase[1]				
	q. 3 months until PD or subsequent treatment for myeloma	At PD or subsequent treatment for myeloma	After PD or subsequent treatment for myeloma q. 6 months	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence

1. If a patient is still alive 2 years after registration, no further follow-up is required.

5.0 Grouping Factor: None

6.0 Registration Procedures

6.1 Registration Procedures

6.11 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."

6.12 Correlative Research: (See Section 14.)

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

6.13 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

6.14 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 [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.

6.15 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research of Multiple Myeloma at Mayo.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems.
- Patient has/has not given permission for MCCC to give his/her sample(s) to researchers at other institutions.

6.16 Treatment on this protocol must commence at a Mayo Clinic Institution, under the supervision of a hematologist.

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

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

6.19 All required baseline symptoms (see Section 10.61) must be documented and graded.

6.19a Blood draw kit is available on site, if applicable (see Section 14).

6.2 Study Conduct

The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating patients; the protocol and any amendments will be subject to approval by the designated IRB prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

7.0 Protocol Treatment

7.1 Treatment Schedule

Cycle length: 84 days.

Agent	Route	Dose	Day	Retreatment
Ixazomib	PO	4 mg	1, 8, 15, 29, 36, 43, 57, 64, 71	Every 84 days
Pembrolizumab	IV	200mg	Day 1, 22, 43, 64	Every 84 days
Dexamethasone	PO	40 mg	1, 8, 15, 29, 36, 43 57, 64, 71	Every 84 days

7.2 For this protocol, the patient must return to the consenting institution (Mayo Clinic) for evaluation at least every 21days (± 1 day). Treatment by a local medical doctor (LMD) is not allowed. Note: If patient is stable after 2 cycles, physical exam can be reduced to Weeks 1 and 7 of each cycle.

7.3 Patients are allowed to collect stem cells after 1 cycle of initial therapy. Stem cells can be collected using standard institutional protocols. Any delay beyond 4 weeks should be discussed with the study PI prior to reinitiating protocol therapy.

7.4 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 Dexamethasone (Cycles 1-4, maximum of 1 year)

- Dexamethasone may be self-administered by the subject on an outpatient basis.
- Missed doses of dexamethasone will not be made up. Procedures for dose reductions and delays are summarized in Section 8.0.
- Dexamethasone is commercially available. Accurate records will be kept in the source documents of all drug administration (including dispensing and dosing).

8.0 Dosage Modification Based on Adverse Events

Individual drugs can be dose reduced as per the table below depending on the adverse event attribution of possible, probable, or definite. 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.

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

8.1 Dose Levels for each drug in the combination.

	Ixazomib (Days 1, 8, 15, , 29, 36, 43, 57, 64, 71)	**Pembrolizumab (200 mg/dose)**	**Dexamethasone (Days 1, 8, 15, 29, 36, 43, 57, 64, 71)**
Starting dose	4 mg	Day 1, 22, 43, 64	40 mg
-1	3 mg	Day 1 and 43	20 mg
-2	2.3 mg	Discontinue	12 mg

*See Table 8.2 below

Note: If ixazomib is discontinued, the patient will discontinue pembrolizumab and dexamethasone and go to event monitoring.

8.11 Instruction for initiation of a new cycle of therapy

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

- The ANC is ≥1000/μL
- The platelet count is ≥75,000/μL
- Any other non-hematologic drug-related (possible, probable, or definite) 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, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate.

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.

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

CTCAE System/Organ/Class (SOC)	Adverse Event	Omit Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Endocrine disorders	Endocrine disorders – Other, specify: Hypophysitis	2-4	AE resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Endocrine disorders	Hyperthyroidism	3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue
Endocrine disorders	Hypothyroidism	2	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted
Gastrointestinal disorders	Diarrhea or Colitis	2-3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue
General disorders and administration site conditions	Infusion related reaction	2[b]	AE resolves to Grade 0-1	Permanently discontinue if AE develops despite adequate premedication
		3-4	Permanently discontinue	Permanently discontinue
Investigations	Aspartate aminotransferase (AST) increased or Alanine aminotransferase (ALT) increased or Blood bilirubin increased	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose
		3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Metabolism and nutrition disorders	Glucose intolerance (Type 1 diabetes mellitus [if new onset]) or Hyperglycemia	3-4	Omit pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients are clinically and metabolically stable

CTCAE System/Organ/Class (SOC)	Adverse Event	Omit Treatment for Grade	Timing for Restarting Treatment	Treatment Discontinuation
Renal and urinary disorders	Acute kidney injury or Chronic kidney disease (e.g., Renal failure or Nephritis)	2	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		3-4	Permanently discontinue	Permanently discontinue
Respiratory, thoracic and mediastinal disorders	Pneumonitis	2	Hold pembrolizumab until AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		3-4 or Recurrent 2	Permanently discontinue	Permanently discontinue
Cardiac disorders	Myocarditis	1-2	Hold pembrolizumab until AE resolves to Grade 0-1	Based on severity of AE administer corticosteroids
		3-4	Permanently discontinue	Permanently discontinue
	All Other Drug-Related Adverse Events[c]	3	AE resolves to Grade 0-1	AE does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
		4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

* Located at [redacted]

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

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

8.3 Dose modifications for Ixazomib based on adverse events during a cycle

CTCAE System/Organ/ Class (SOC)*	ADVERSE EVENT	ACTION**
Investigations	Neutrophil count decreased <1.0 x 10^9/L or Neutrophil count decreased >1.0 × 10^9/L (up to LLN) and Fever (temperature >38.5°C) or Platelet count decreased <30 × 10^9/L	Days 2-84: Ixazomib dose should be omitted on Days 1, 8, 15, 29, 36, 43, 57, 64, 71 as applicable Complete blood count (CBC) with differential should be followed weekly If ANC is ≥1.0 × 10^9/L and/or platelet counts ≥30 × 10^9/L, ixazomib may be reinitiated with 1 dose level reduction. The subsequent cycle will use the reduced dose.
Nervous System Disorders	Newly developed peripheral sensory neuropathy Grade 1 with pain or Peripheral sensory neuropathy Grade 2	Omit until resolution to Grade <1 or baseline No dose reduction necessary for this grade
	Peripheral sensory neuropathy with pain Grade 2 or Peripheral sensory neuropathy Grade 3	Omit ixazomib until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate ixazomib at the next lower dose level.
	Peripheral sensory neuropathy Grade 4	Discontinue ixazomib. Peripheral neuropathy should be monitored until toxicity resolves or returns to baseline.
Skin and subcutaneous tissue disorders	Rash, maculo-papular, ≥Grade 2	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.
	Any other skin AE, Grade 4	Discontinue ixazomib and remove patient from all study treatment
	Any other Grade 3 attributable adverse event except: • Nausea and/or Vomiting Grade 3 in the absence of optimal anti-emetic prophylaxis • Diarrhea Grade 3 that occurs in the absence of optimal supportive therapy • Fatigue Grade 3 • Anemia • White blood cell decreased • Lymphocyte count decreased	Omit ixazomib depending on the attribution, 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
	Any other Adverse Events Grade 4	Consider permanently discontinuing ixazomib – Exception if the investigator determines the patient is obtaining a clinical benefit

* Located at [redacted]

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

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

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

CTCAE System/Organ/Class (SOC)	ADVERSE EVENT	AGENT	ACTION**
Gastrointestinal disorders	Dyspepsia Grade 1 or 2 or Duodenal ulcer Grade 1 or 2 or Gastric ulcer Grade 1 or 2 or Gastritis Grade 1 or 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 or Duodenal ulcer ≥Grade 3 or Gastric ulcer ≥Grade 3 or 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 dexamethasone and do not resume
	Pancreatitis ≥Grade 3	Dexamethasone	Discontinue dexamethasone and do not resume
General disorders and administration site conditions	Edema limbs ≥Grade 3 or Edema trunk ≥Grade 3	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
Metabolism and nutrition disorders	Hyperglycemia ≥Grade 3	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.
Musculoskeletal and connective tissue disorders	Generalized muscle weakness ≥Grade 2	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
Psychiatric disorders	Confusion Grade ≥2 OR/And Anxiety 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.

* Located at [redacted]

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

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

9.0 Ancillary Treatment/Supportive Care

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 10.1.

9.1 Oral hydration

Patients are encouraged to drink at least 6 to 8 cups of liquid per day.

9.2 Disallowed concurrent treatment

The following treatments are not permitted during the trial:

- Any other investigational treatment
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Any external beam radiotherapy
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day

9.3 Nausea and/or vomiting

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

9.4 Blood products and growth factors

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

9.5 Diarrhea and Ixazomib

Prophylactic antidiarrheals should be used in this protocol. Diarrhea occurring despite the prophylaxis 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. Additional doses of loperamide at 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.

Please monitor patients carefully for development of ileus.

9.6 Renal failure and Ixazomib

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

9.7 Herpes Zoster prophylaxis

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

9.8 Prohibited medications

9.81 Prohibited enzyme inducers

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided, unless there is no appropriate alternative medication for the patient's use. (Rationale: If there were to be a drug-drug interaction with an inducer, ixazomib exposure would be less - so there is a reduced chance of an adverse event. However, there may be less chance for an antitumor effect, but that is not an absolute reason to be taken off study):

Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital.

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

9.83 Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Radiation therapy
  - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

9.9a Erythematous Rash with or without Pruritus

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

Symptomatic measures such as antihistamines or corticosteroids (oral or topical) have been successfully used to manage rash and have been used prophylactically in subsequent cycles. The use of a topical, IV, or oral steroid (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 section 8.3 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 Section 8). 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 section 4.0 with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Section 8). Therapy can be reinitiated at a reduced level upon recovery of ANCs.

9.9d Fluid Deficit

Vitals should be assessed prior to start of each cycle as per Table 4.1. Dehydration should be avoided since ixazomib may cause vomiting, diarrhea, and dehydration. Patients should be encouraged to maintain adequate fluid intake. Acute renal failure has been reported in patients treated with ixazomib, commonly in the setting of the previously noted gastrointestinal toxicities and dehydration. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

9.9e Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been reported with ixazomib. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the

setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial. Fluid deficit should be corrected before initiation of study drug and as needed during treatment to avoid dehydration.

9.9f Posterior Reversible Encephalopathy Syndrome

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

9.9g Transverse Myelitis

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

9.9h Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance (as outlined below). Refer to Table 8.2 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

- **Pneumonitis**:
  - For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
  - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis,** administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis,** treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)**
  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

- **Hypophysitis**:
  - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
  - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
  - **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism

- Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.
- **Renal Failure or Nephritis**:
  - For **Grade 2** events, treat with corticosteroids.
  - For **Grade 3-4** events, treat with systemic corticosteroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

  Table 9.1. below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 9.9h1 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

9.9i Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.
For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).
Female subjects will be considered of non-reproductive potential if they are either:
(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in

women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
OR
(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
OR
(3) has a congenital or acquired condition that prevents childbearing.
Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:
(1) practice abstinence† from heterosexual activity;
OR
(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:
Single method (one of the following is acceptable):
• intrauterine device (IUD)
• vasectomy of a female subject's male partner
• contraceptive rod implanted into the skin

Combination method (requires use of two of the following):
• diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
• cervical cap with spermicide (nulliparous women only)
• contraceptive sponge (nulliparous women only)
• male condom or female condom (cannot be used together)
• hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

10.0 Adverse Event (AE) Monitoring and Reporting

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):

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:
[redacted]

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.

NOTE: *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. Refer to protocol or IB for reporting needs.

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).

[redacted]

10.32 EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting

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).*

*Report any clinically important increase in the rate of a serious suspected adverse reaction (at your study site) over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be expeditedly reported.
Blood and lymphatic system disorders	Anemia	≤ Grade 4
Gastrointestinal	Diarrhea	≤ Grade 3
	Nausea	≤ Grade 3
	Vomiting	≤ 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 count 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 following hospitalizations are not considered to be SAEs because there is no "adverse event" (*i.e.*, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (*e.g.*, battery replacement) that was in place before study entry

- Hospitalization, or other serious outcomes for signs and symptoms of progression of the cancer.]

10.4 Expedited Reporting Requirements for IND Agents

10.41 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 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

[redacted] investigational agents or commercial/investigational agents on the same arm.

[redacted]

10.43 Reporting of re-occurring SAEs

ALL SERIOUS adverse events that meet the criteria outlined in table10.41 MUST be immediately reported to the sponsor within the timeframes detailed in the corresponding table. This reporting includes, but is not limited to SAEs that re-occur again after resolution.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS)

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 Report Form

[redacted] The Mayo Clinic Compliance Unit will review and process the submission to the Mayo Clinic IRB and work with the IND Coordinator for submission to FDA.

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. Include this form: [redacted]

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.

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.
Grading is per CTCAE v4.0 **unless** alternate grading is indicated in the table below:

CTCAE SYSTEM/ORGAN/CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Gastrointestinal Disorders	Baseline # of stools	X	
	Constipation		X
	Diarrhea		X
	Nausea	X	X
	Vomiting	X	X
General disorders and administration site conditions	Fatigue	X	X
Infections and infestations	Sepsis	X	X
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Skin and subcutaneous tissue disorders	Rash, maculo-papular	X	X

10.62 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.6:

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 Event Reporting Instructions

10.81 Merck

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described above.

Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor and within 2 working days hou [redacted]

Reporting of Pregnancy and Lactation to Merck

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted]

Immediate Reporting of Adverse Events to Merck

Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;

- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is another important medical event

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: [redacted]

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, or other local regulators. Investigators will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., [redacted] at the time of submission to FDA.

All subjects with serious adverse events must be followed up for outcome.

Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. [redacted] Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined above - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; [redacted] regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

10.82 Takeda

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 Takeda 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 Takeda 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 Takeda 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, Yi Lin, 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 Takeda 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 Takeda Pharmacovigilance.

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

The SAE report must include at minimum:

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

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

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 [redacted]

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Takeda 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 Takeda 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 Takeda Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

SAE and Pregnancy Reporting Contact Information

[redacted]

Suggested Reporting Form:

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

Product Complaints

A product complaint is a verbal, written, or electronic expression that implies

dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

For Product Complaints

- [redacted]
  - E-mail: [redacted]
  - FAX: [redacted]
  - Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

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

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

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

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

Suggested Pregnancy Reporting Form:

Pregnancy Report Form (provided by Takeda)

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 be 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

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.

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				X[3]

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**
marrow ≥30% plasma cells				

[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.

IMWG MRD NEGATIVITY CATEGORY	**RESPONSE CRITERIA [a]**
Sustained MRD	MRD negativity in the marrow (Next Generation Flow (NGF) or Next

IMWG MRD NEGATIVITY CATEGORY	RESPONSE CRITERIA [a]
	Generation Sequencing (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]	• 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 protein *and* reduction in 24-hour urine M-protein by 50-89% which

IMWG MRD NEGATIVITY CATEGORY	RESPONSE CRITERIA [a]
	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 the table. 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.

12.0 Descriptive Factors

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

12.2 Number of lines of prior therapy: 1 vs. 2 vs. ≥ 3

12.3 Prior SCT: yes vs. no

13.0 Treatment/Follow–up Decision at Evaluation of Patient

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

13.2 Patients who develop progressive disease or start alternate therapy while receiving therapy will go to the event-monitoring phase per Section 4.2.

13.3 Patients who go off protocol treatment for reasons other than PD will go to the event-monitoring phase per Section 4.2.

13.4 Patients who are discontinued from therapy for an unacceptable adverse event(s) will be followed until resolution or stabilization of the AE(s).

13.5 Criteria for Patient Withdrawal from Study Treatment

Patients may be withdrawn from the study 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 at least 1 month apart).
- 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 if a patient withdraws from the trial early.

13.6 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 guidances 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.

13.7 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 4.2 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.

13.8 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 4.2 of the protocol.

13.9 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 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol:

Bone marrow collection schedule:

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)	Baseline (Prior to cycle 1)	Cycle 2 Day 1	At Progression	Document CR	Process at site? (Yes or No)	Temperature/ Conditions for Storage /Shipping
Immune markers	Mandatory	Marrow	ACD (yellow)	6 ml (3)	X	X	X	X	No	Kool-Pak
Immune markers	Mandatory	Marrow	EDTA (purple)	4 ml (1)	X	X	X	X	No	Kool-Pak

Blood collection schedule:

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)	Cycle 1 Days 1, 22 (pre dose)	Every Cycle Day 1 (pre dose)	At progression	Document CR	Process at site? (Yes or No)	Temperature/ Conditions for Storage /Shipping
Immune markers	Mandatory	Blood	Heparin (green)	10 ml (5)	X	X	X	X	No	Kool-Pak
Immune markers	Mandatory	Blood	EDTA (purple)	6 ml or (1)	X	X	X	X	No	Kool-Pak

14.2 Collection and Processing:

Samples are to be shipped the same day as they are collected. No processing is required at the sites.

14.3 Shipping and Handling

14.31 Kits

14.311 Kits will be used for this study (except in Rochester). Kits will contain supplies and instructions for collection, processing and shipping specimens

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

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

14.32 Shipping for bone marrow samples

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

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

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

Predolin Foundation Biobank

[redacted]

14.32 Shipping for blood samples

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

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

[redacted]

14.4 Background and Methodology

14.41 PDL1 expression

PDL1 expression will be measured on the myeloma cells in the bone marrow (CD138, 38 positive) by using flow cytometry. The expression will also be determined on other cell types in the bone marrow.

14.42 Measures of immune activation

The "global" impact of therapy on immune cell subsets will be ascertained by immunophenotypic analysis of PBMCs for subsets of T, B, NK cells, monocytes and dendritic cells (DC) and their activation status using commercially available monoclonal antibodies directed at the following antigens: CD3, CD4, CD8, CD11c, CD14, C16, CD19, CD20, CD25, CD45RA/RO, CD56, CD69, CD63L, CD80, CD83, CD86, CD123, DR. The flow cytometric analysis will also be performed on the bone marrow samples.

Activation of DC and subsequent modulation of the immune response caused by treatment with Ixazomib may directly or indirectly alter the cytokines present in plasma. The BioRad human 27-plex cytokine panel will be used for the measurements of plasma concentrations of IL-1β, IL-1rα, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, basic FGF, eotaxin, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1, MIP-1α, MIP-1β, PDGF, RANTES, TNF-α, and VEGF.

14.43 Samples for future studies

An aliquot of CD138 sorted MM cells and CD138 negative cells will be stored in DMSO for future studies. An aliquot of peripheral blood plasma as well as PBMC will be stored for potential studies in future.

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 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 mg, 4 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 Millennium 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. It is recommended to wear gloves and protective garments during preparation when dispensed in clinic.

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 Pembrolizumab (MK-3475, SCH 900475, Keytruda®)

15.21 **Background**: Pembrolizumab is a potent humanized IgG4 monoclonal antibody with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and PD-L2. Based on preclinical *in vitro* data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

15.22 **Formulation**
Pembrolizumab is available as a liquid 25 mg/mL, 100 mg/vial.

15.23 **Preparation and storage**:
Drug concentrate is further diluted with normal saline (or 5% dextrose) in Vials should be stored in the refrigerator at temperatures between 2-8°C. Drug concentrate is further diluted with normal saline (or 5% dextrose) in the concentration range of 1 to 10 mg/mL i The infusion solution in the IV bag should be immediately administered. Diluted pembrolizumab solutions may be stored at room temperature for a cumulative period of up to 6 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. The product can also be stored under refrigeration at 2°C to 8°C for no more than 96 hours from the time of dilution. If refrigerated, the diluted solution must be allowed to come to room temperature prior to administration. The solution must be discarded after 6 hours at room temperature or 96 hours under refrigeration.

15.24 **Administration:** Pembrolizumab is administered by intravenous infusion over 30 minutes via a 0.22 micron in-line filter. The final infusion volume must be between 1 and 10 mg/mL. Maximum rate of infusion should not exceed 6.7 mL/minute through a peripheral or indwelling catheter. Flush the line with 0.9% NaCL following the completion of the infusion.

15.25 **Pharmacokinetic information**:
a) Absorption – Because pembrolizumab is administered intravenously, it is immediately and completely bioavailable. Steady-state concentrations of

pembrolizumab are reached by 16 weeks of repeated dosing with a Q3W regimen and the systemic accumulation is 2.1 fold. The peak concentration, trough concentration, and area under the plasma concentration versus time curve at steady state of pembrolizumab increased dose proportionally in the dose range of 2 to 10 mg/kg Q3W.
b) Distribution – Pembrolizumab has a limited volume of distribution.
c) Excretion - is approximately 23% lower after achieving maximal change at steady state compared with the first dose The terminal elimination half-life (t½) is estimated to be ~26 days at steady state.
d) Metabolism - Pembrolizumab is catabolized through non-specific pathways; metabolism does not contribute to its CL.

15.26 **Potential Drug Interactions:** There are no known significant drug interactions.

15.27 **Known potential toxicities**:
Very common known potential toxicities, ≥ 10%:
Gastrointestinal disorders: diarrhea, nausea, abdominal pain
Skin and subcutaneous tissue disorders: rash, pruritis
General disorders and administration site conditions: fatigue

Common known potential toxicities, ≥1% to < 10%:
Blood and lymphatic system disorder: anemia
Immune system disorders: infusion related reaction
Endocrine disorders: hyperthyroidism, hypothyroidism
Metabolism and nutrition disorders: decreased appetite
Nervous system disorders: headache, dizziness, dysgeusia
Respiratory, thoracic, and mediastinal disorders: pneumonitis, dyspnea, cough

Gastrointestinal disorders: colitis, vomiting, constipation, dry mouth
Skin and subcutaneous tissue disorders: severe skin reactions, vitiligo, dry skin, erythema
Musculoskeletal and connective disuse disorders: arthralgia, jyositis, musculoskeletal pain, arthritis, pain in extremity

General disorders and administration site conditions: asthenia, edema, pyrexia, influenza like illness, chills
Investigations: alanine aminotransferase increased, aspartate aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased

Less common known potential toxicities, ≥0.1% to <1%:
Infusion related reactions
Blood and lymphatic system disorders: neutropenia, thrombocytopenia, leukopenia, lymphopenia, eosinophilia
Endocrine disorders: hypophysitis, adrenal insufficiency, thyroiditis, hypopituitarism

Metabolism and nutrition disorders: type I diabetes mellitus, hyponatremia, hypokalemia, hypocalcemia
Psychiatric disorders: insomnia, confusional state
Nervous system disorders; epilepsy, lethargy, peripheral neuropathy

Eye disorders: uveitis, dry eye
Cardiac disorders: myocarditis, atrial fibrillation
Vascular disorders: hypertension
Gastrointestinal disorders: pancreatitis, dysphagia
Hepatobiliary disorders: hepatitis
Skin and subcutaneous tissue disorders: lichenoid keratosis, psoriasis, alopecia, dermatic, dermatitis acneiform, eczema, hair color changes, papule
Musculoskeletal and connective tissue disorders: tenosynovitis, myelitis
Renal and urinary disorders: nephritis, acute kidney injury
Investigations: blood bilirubin increased, amylase increased, hypercalcemia

Rare known potential toxicities, <0.1% (Limited to important or life-threatening):
Blood and lymphatic system disorders: immune thrombocytopenic purpura, hemolytic anemia
Immune system disorders: sarcoidosis
Nervous system disorders: Guillain-Barre syndrome, myasthenic syndrome
Gastrointestinal disorders: small intestinal perforation
Skin and subcutaneous tissue disorders: toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema nodosum

The risk profile for pembrolizumab also includes two important potential risks: a) myasthenic syndrome, and b) an increased risk of severe complications (such as early severe graft versus host disease and venoocclusive disease) of allogeneic transplant in patients with hematologic malignancies who have previously been treated with PD-1 inhibitors.

Patients with multiple myeloma who were treated with pembrolizumab in combination with either pomalidomide or Lenalidomide and dexamethasone, had an increased number of serious side effects and deaths as compared to patients who received only dexamethasone and either pomalidomide or Lenalidomide. The benefit-risk profile is unfavorable for the combination of pembrolizumab, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma, and the combination of pembrolizumab, Lenalidomide, and dexamethasone in newly diagnosed treatment-naïve multiple myeloma.

Post marketing reports identified Vogt-Koyanagi-Harada syndrome and hemophagocytic lymphohistiocytosis.

15.28 **Drug procurement:** Pembrolizumab will be provided free of charge to study participants by Merck.

15.29 Nursing guidelines

15.291 Pembrolizumab side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids.

15.292 Diarrhea can be seen however is less common than that seen with anti-CTLA-4 agents. However it can be severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

15.293 Rash/pruirits/dermatitis is seen. Patients should report any rash to the study team. Treat per section 9.0 and monitor for effectiveness.

15.294 Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

15.295 Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

15.296 Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are seen with this agent. Patients may present only with the vague sense of fatigue and "not feeling well" . Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

15.197 Patients who are started on steroid therapy for any side effects of pembrolizimab toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

15.298 Fatigue is common and may or may not be associated with immune related side effects. Assess patient's fatigue level prior to each cycle of therapy and report any changes to the study team.

15.299a Patients should avoid receiving live vaccines within 30 days of study drug administration or per other study guidelines.

15.299b Patients who have undergone an allogenic bone marrow transplant, have an increased risk of severe complications including early GVHD, and venoocclusive disease, if they have previously been treated with pembrolizumab

15.299c Myocarditis has been reported and associated with pembrolizumab. Instruct patients to report chest pain, SOB, or dyspnea to study team immediately and/or seek emergency medical attention.

15.299dAutoimmune hematologic disorders including ITP and hemolytic anemia have been reported. Monitor blood counts closely and report any abnormalities to the study team.

15.299e Rare neurologic disorders including Guillian-Barre syndrome and myasthenia gravis have been reported. Instruct patients to report any neurologic symptoms including weakness, parasthesias or numbness, tingling to the study team immediately.

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, 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 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 Pembrolizumab with ixazomib and dexamethasone for treatment of relapsed multiple myeloma patients requiring therapy. This study is designed to assess the overall response rate associated with therapy with pembrolizumab added to standard doses of ixazomib and dexamethasone in patients with relapsed multiple myeloma using a single stage phase II study design with an interim analysis.

16.11 Endpoint: The primary endpoint of the trial is the overall response rate. A success will be defined as a PR or better noted as the objective status on two consecutive evaluations. Response will be evaluated using all cycles. Throughout Section 16.0, response will be considered synonymous with "success", unless specified otherwise.

16.12 Sample Size: The single-stage study design with an interim analysis to be used is fully described below. A minimum of 14 and a maximum of 37 evaluable patients will be accrued in the 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 for a maximum of 41 patients. All patients meeting the eligibility criteria who have signed consent and received at least one dose of treatment will be considered evaluable for response, with the exception of patients who are determined to be a major violation.

16.13 Accrual Rate and Study Duration: The anticipated accrual rate is 2-3 evaluable multiple myeloma patients per month. At this rate, it will likely take about 1.5 years to enroll the patients. The maximum total study duration is expected to be approximately 4.5 years, or until the last patient accrued has been observed for at least 3 years. The earliest date anticipated for presentation of results is at approximately 2 years, or when the last patient accrued has been observed for at least 6 months.

16.2 Statistical Design:

16.21 Decision Rule:

A combination of ixazomib plus dexamethasone, an oral regimen, is effective for the treatment of relapsed multiple myeloma, with a response rate of 31% seen in a previous study that included 35 patients treated at the standard doses. An increase in the overall response rate with the addition of pembrolizumab to Ixazomib plus dexamethasone would be of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 30%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 50%. The following one-stage design with an interim analysis is based on a Simon optimum design and requires 37 evaluable patients to test the null hypothesis that the true success proportion in this patient population is at most 30%.

16.211 Interim Analysis: Enter 14 evaluable patients into the study. If 4 or fewer successes are observed in the first 14 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 5, we will continue accrual.

16.212 Final Decision Rule: Enter an additional 23 evaluable patients into the study. If 14 or fewer successes are observed in the first 37 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 15, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

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 16.34.

16.214 NOTE: We will not suspend accrual at the interim analysis to allow the first 14 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an adverse events stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients

16.22 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .095, i.e. there is a 9.5% chance of finding the drug to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e. statistical power) and the probability of stopping after the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.30	0.35	0.40	0.45	0.50
Then the probability of declaring that the regimen warrants further study is…	0.095	0.253	0.474	0.694	0.853
And the probability of stopping after the interim analysis is …	0.584	0.423	0.279	0.167	0.090

16.23 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

16.31 Primary Outcome Analyses:

16.311 Definition: The primary endpoint in this trial is the overall response rate. A success is defined as a PR or better noted as the objective status on two consecutive evaluations. Response will be evaluated using all cycles. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, with the exception of patients determined to be a major violation.

16.312 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.

16.32 Secondary Outcome Analyses

16.321 The ≥VGPR response rate with pembrolizumab added to Ixazomib and dexamethasone will be estimated by the number of patients who achieve a VGPR, CR, or sCR at any time divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success rate will be calculated.

16.322 The complete response rate with pembrolizumab added to Ixazomib and dexamethasone will be estimated by the number of patients who achieve a CR or sCR at any time divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success rate will be calculated.

16.323 Survival time is defined as the time from date of first treatment to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier[7].

16.324 Progression-free survival is defined as the time from date of first treatment to the earliest date of documentation of disease progression or death due to any cause. Patients who receive subsequent treatment for myeloma before disease progression will be censored on the date of their last disease assessment prior to initiation of the subsequent treatment. Transplant will not be considered subsequent treatment. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier

16.325 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 PDL-1 expression on myeloma cells and non-tumor cell compartments from the bone marrow will be assessed at baseline. Each measure will be summarized descriptively by median, min, max and interquartile range.

16.332 Markers of T-cell activation and exhaustion will be summarized descriptively by median, min, max, and interquartile range at each time point. Patterns over time will be summarized by absolute difference or relative change. Changes across time will be assessed using paired analyses, including Wilcoxon signed rank tests. Jitplots will be used to visually examine differences between groups for continuous factors.

16.333 NK cell function and numbers will be summarized descriptively by median, min, max, and interquartile range at each time point. Patterns over time will be summarized by absolute difference or relative change. Changes across time will be assessed using paired analyses, including Wilcoxon signed rank tests. Jitplots will be used to visually examine differences between groups for continuous factors.

16.34 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 endpoint estimates and confidence intervals.

16.4 Early Safety Analysis

An early safety analysis will be performed after the first 6 patients have been accrued to the study and observed for at least 42 days. Accrual will be temporarily halted while these patients are evaluated. If 2 or more of the first 6 patients experience a DLT as defined below, then accrual to the study will continue to be temporarily halted while the study team determines if changes to the dosing schedule are warranted.

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

- Any ≥Grade 4 neutrophil count decrease or platelet count decrease that persists >7 days
- Any ≥Ggrade 3 infections
- ≥Grade 3 erythema multiforme, ulceration, or urticarial that does not resolve to ≤Grade 2 within 3 weeks
- ≥Grade 3 bronchial obstruction, pneumonitis, or wheezing
- ≥Grade 3 allergic reaction or autoimmunity
- All other ≥Grade 3 non-hematologic toxicities (with the exception of electrolyte abnormalities that are reversible and asymptomatic) that does not resolve to ≤Grade 2 in ≤72 hours despite optimal supportive medications

16.5 Data & Safety Monitoring:

16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety

Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.52 Adverse Event Stopping Rules

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

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

- if 2 or more patients in the first 6 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

- if after the first 6 patients have been treated, 40% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment.

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

16.6 Results Reporting on ClinicalTrials.gov:

At study activation, this study will have been registered within the [redacted] website. The Primary and Secondary Endpoints along with other required information for this study will be reported on [redacted] For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time all patients registered have been observed for 12 months.

16.7 Inclusion of Women and Minorities

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

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

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

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	0	1	0	1
Not Hispanic or Latino	14	26	0	40
Ethnic Category: Total of all subjects*	**14**	**27**	**0**	**41**
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	1	1	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	13	26	0	39
Racial Category: Total of all subjects*	**14**	**27**	**0**	**41**

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

18.5 Supporting documentation

This study requires supporting documentation for evidence of response to study therapy and progression after study therapy (sCR, MRD negative, PD).

18.6 Labelling of materials

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

18.7 Incomplete materials

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

18.8 Overdue lists

A list of overdue materials is automatically available to each site at any time. The appropriate co-sponsor/participant will be responsible to submit the overdue material.

18.9 Corrections forms

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

19.0 Budget

19.1 Costs charged to patient: routine clinical care, and dexamethasone

19.2 Tests to be research funded: None

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

20.0 References

1. Richardson P, Jagannath S, Schlossman R, et al. A Multi-center, Randomized, Phase 2 Study to Evaluate the Efficacy and Safety of 2 CDC-5013 Dose Regimens When Used Alone or in Combination with Dexamethasone (Dex) for the Treatment of Relapsed or Refractory Multiple Myeloma (MM). *Blood*. 2003;102:235a.
2. Lacy M, Gertz M, Dispenzieri A, et al. Ixazomib Plus Dexamethasone (Rev/Dex) in Newly Diagnosed Myeloma: Response to Therapy, Time to Progression, and Survival. *Blood*. 2006;108(11):798-.
3. Rajkumar SV, Jacobus S, Callander N, et al. Phase III trial of Ixazomib plus high-dose dexamethasone versus Ixazomib plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): a trial coordinated by the Eastern Cooperative Oncology Group. *J Clin Oncol 2007 ASCO Annual Meeting Abstracts* 2007;25 (18S):LBA8025.
4. Weber DM, Chen C, Niesvizky R, et al. Ixazomib plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357(21):2133-2142.
5. Dimopoulos M, Spencer A, Attal M, et al. Ixazomib plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357(21):2123-2132.
6. Rajkumar SV, Jacobus S, Callander NS, et al. Ixazomib plus high-dose dexamethasone versus Ixazomib plus low-dose dexamethasone as initial therapy for newly diagnosed multiple myeloma: an open-label randomised controlled trial. *Lancet Oncol*. 2010;11(1):29-37.
7. Kaplan E, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.

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 [redacted]

From [redacted]

Appendix II PATIENT MEDICATION DIARY

Name _____ Study ID _____

Please complete this diary on a daily basis. Write in the amount of the dose of 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. The study drugs should be taken on an empty stomach (no food or drink) at least 1 hour before or at least 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 or dexamethasone, please record this information.

Week of: _____

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

Week of: _____

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

Week of: _____

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

Week of: _____

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

Week of: _____

Study Drug	Day 29	Day 30	Day 31	Day 32	Day 33	Day 34	Day 35
Ixazomib							
Dexamethasone							

Week of: _____

Study Drug	Day 36	Day 37	Day 38	Day 39	Day 40	Day 41	Day 42
Ixazomib							
Dexamethasone							

Week of: _____

Study Drug	Day 43	Day 44	Day 45	Day 46	Day 47	Day 48	Day 49
Ixazomib							
Dexamethasone							

Week of:

Study Drug	Day 50	Day 51	Day 52	Day 53	Day 53	Day 55	Day 56
Ixazomib							
Dexamethasone							

Week of: _____

Study Drug	Day 57	Day 58	Day 59	Day 60	Day 61	Day 62	Day 63
Ixazomib							
Dexamethasone							

Week of:

Study Drug	Day 64	Day 65	Day 66	Day 67	Day 68	Day 69	Day 70
Ixazomib							
Dexamethasone							

Week of: _____

Study Drug	Day 71	Day 72	Day 72	Day 74	Day 74	Day 76	Day 77
Ixazomib							
Dexamethasone							

Week of:

Study Drug	Day 78	Day 79	Day 80	Day 81	Day 82	Day 83	Day 84
Ixazomib							
Dexamethasone							

My next scheduled visit is: _____

If you have any questions, please call: _____