Mayo Clinic Cancer Center

Phase 1 / 2 trial of Idasanutlin in combination with Ixazomib and dexamethasone in patients with 17p deleted, relapsed multiple myeloma

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MMRC Study: MMRC-061
Takeda Study: X16066
Roche Study: NP29909
IND: 128,400

Drug Availability
Commercial Agents: Dexamethasone
Drug Company Supplied: Ixazomib (***Takeda/Millennium***), Idasanutlin (***Roche***)

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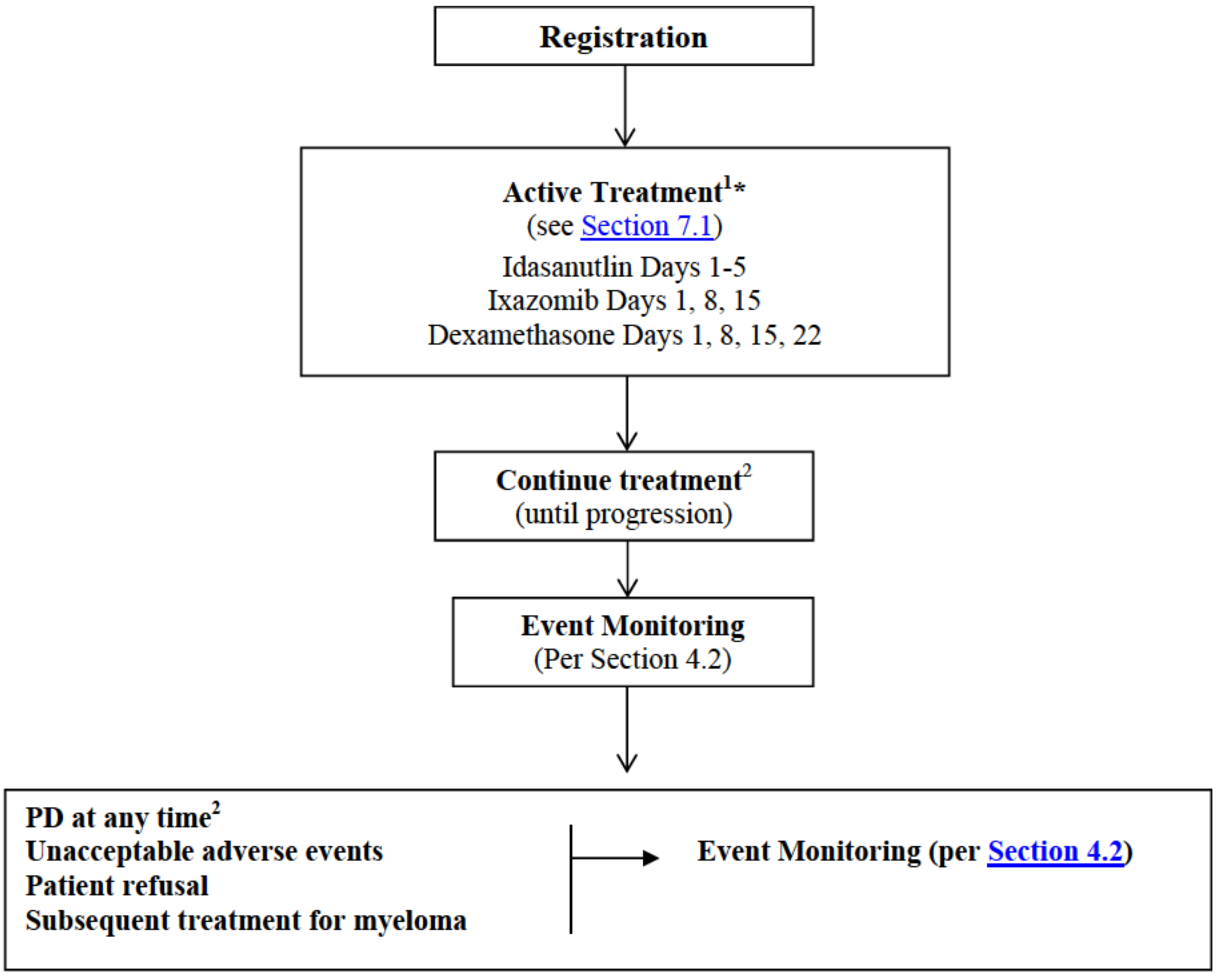
Protocol Resources

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/ interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted] Specialist Phone: [redacted]
Protocol document, consent form, regulatory issues	Mayo Clinic Cancer Center Clinical Research Office (MCCC CRO) Email: [redacted] Mayo Clinic Staff: See Protocol Catalog for current RPS assignment [redacted]
Serious Adverse Events	[redacted] Phone: [redacted]
Biospecimens	[redacted] Hematology Lab Phone: [redacted]

Table of Contents

Schema

Open to Phase II as of Addendum 4



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

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

Generic name: Ixazomib Brand name(s): Ninlara® Mayo Abbreviation: MLN9708 Availability: Takeda/Millennium	Generic name: Dexamethasone Brand name(s): Decadron® Mayo Abbreviation: DXM Availability: Commercial	Generic name: Idasanutlin Brand name(s): N/A Mayo Abbreviation: RO5503781 Availability: Roche

1.0 Background

1.1 ***Multiple Myeloma:*** Multiple myeloma (MM) is an incurable malignancy arising from post germinal center, terminally differentiated plasma cells, characterized by an excess of monotypic plasma cells in the bone marrow, resulting in elevated levels of monoclonal immunoglobulins (Ig) in the serum and/or urine. Common clinical sequelae include lytic bone lesions, fractures, myelosuppression, and renal failure. In the United States of America (USA), the estimated annual diagnosed incidence is 22,350, with approximately 100,000 prevalent cases.(Siegel, Naishadham et al. 2013) In Europe, the estimated annual diagnosed incidence is 21,611 with approximately 54,536 prevalent cases.(1998) Multiple myeloma accounts for 10% of all hematologic malignancies and 1% of all malignancies. Advances in high-dose chemotherapy and stem cell transplantation have improved overall survival and event-free disease periods in patients with MM, but relapses are inevitable.(Kumar, Lee et al. 2012, Kumar, Dispenzieri et al. 2013) New therapeutic agents, such as bortezomib and thalidomide analogues, have shown promising clinical benefit in patients with relapsed or refractory disease. Current treatments include combination chemotherapy with regimens using melphalan (Alkeran®), bortezomib (Velcade®), thalidomide (Thalomid®), and lenalidomide (Revlimid®) with and without corticosteroids.(Mikhael, Dingli et al. 2013) Younger patients are consolidated with high-dose therapy (ablative chemotherapy or radiation) with autologous stem cell transplantation (ASCT). Despite these therapeutic advances, MM remains essentially incurable and is associated with high morbidity and mortality.(Palumbo, Bringhen et al. 2006) Multiple myeloma (MM) is a heterogeneous disease with diverse outcomes dictated in large part by the presence of various genetic abnormalities. Genetic abnormalities are seen in the plasma cells in nearly all patients with myeloma, especially when assessed with interphase FISH.(Avet-Loiseau, Attal et al. 2007, Fonseca, Bergsagel et al. 2009) The abnormalities broadly consist of translocations involving the immunoglobulin heavy chain locus on chromosome 14 or trisomies of one or more odd numbered chromosomes, or a combination of the two.(Kumar, Fonseca et al. 2012) Presence of certain genetic abnormalities are associated with a dismal outcome; abnormalities that denote high-risk myeloma. Among these, presence of p53 abnormality in particular is associated with a poor survival, with median overall survival of 3 years or less.(Lopez-Anglada, Gutierrez et al. 2010, Kumar, Fonseca et al. 2012) These patients respond well to initial therapy, but rapidly become refractory to the available therapies and relapse. Studies have suggested that myeloma cells are genomically unstable, and loss of p53 may signal heightened instability. Given the poor outcome seen in these patients even with the most effective regimens, it is imperative we design new approaches to treat these patients.

1.2 ***17p deletion in multiple myeloma:*** Survival of patients with multiple myeloma (MM) has nearly doubled in the previous decade, but nearly a quarter of patients have an aggressive course with median survival of less than 3 years.(Kumar, Rajkumar et al. 2008) Genetic abnormalities are the major determinants of outcome in myeloma and can be broadly grouped into trisomies, translocations involving heavy chain locus on chromosome 14, and monosomies or deletions involving various chromosomes(Avet-Loiseau, Attal et al. 2007, Kumar, Mikhael et al. 2009, Kumar, Fonseca et al. 2012) Trisomies typically involve the odd numbered chromosomes and are associated with good outcome.(Chng, Van Wier et al. 2005) There are five recurrent translocations that can affect the IgH locus resulting in activation of different oncogenes. Among these t(4;14), t(14;16) and t(14;20) are associated with shortened survival.(Bergsagel and Kuehl 2005) Finally, partial deletions or monosomies affecting chromosomes 1, 13, 14, 16 and 17 have been reported. In particular, loss of the short arm of chromosome (17p-) or its monosomy results in loss of the *TP53* gene.(Chng, Price-Troska et al. 2007) This abnormality is seen in approximately 10% of patients at diagnosis and 10-15%

of patients at relapse and results in short response duration to therapy, rapidly becoming resistant to all available therapies and succumbing to the disease within the first 2-3 years after diagnosis.(Neri, Baldini et al. 1993, Drach, Ackermann et al. 1998, Avet-Loiseau, Li et al. 1999, Chang, Qi et al. 2005, Gertz, Lacy et al. 2005, Chng, Price-Troska et al. 2007, Tiedemann, Gonzalez-Paz et al. 2008, Xiong, Wu et al. 2008) Abnormalities of the *TP53* gene have been associated with poor outcome in almost all cancers studied, including hematological cancers and solid tumors. The *TP53* gene is often referred to as the 'guardian of the genome', given its crucial role in induction of apoptosis in cells in the presence of DNA damage. Following DNA damage, *TP53* regulates key processes, including DNA repair, cell-cycle arrest, senescence and apoptosis. This serves to suppress replication and propagation of the cells with the damaged DNA, thus reducing the risk of cancer. In the absence of normal *TP53* function, many cancer therapies do not work well given the inability to induce apoptosis through DNA damage mechanisms. In the majority of tumors, loss of *TP53* function is a result of a mutated *TP53* gene. In sharp contrast, *TP53* abnormalities in MM appear to be related primarily to loss of the gene through an interstitial deletion or monosomy of chromosome 17.(Chng, Price-Troska et al. 2007, Xiong, Wu et al. 2008) The lack of mutations involving the *TP53* gene in MM, unlike other cancers, opens up new therapeutic potential in terms of modulation of *TP53* gene function. In normal cells, p53 levels are regulated by MDM2, a RING domain protein, through a negative feedback loop. When nuclear p53 levels are elevated, transcription of the MDM2 gene occurs leading to increased cellular levels of mdm2 protein, which in turn binds to p53 and blocks its transactivation domain. MDM2 also has a p53- specific E3 ubiquitin ligase activity that leads to ubiquitin-dependent degradation of p53. Therefore, blocking the p53-MDM2 interaction can enhance levels of p53 in the presence of a functional p53 gene and particularly in the setting of myeloma, may be able to compensate for the loss of one of the alleles. Pre-clinical studies with nutlin-class drugs have demonstrated potent in vitro activity for this mechanism in myeloma. (Stuhmer, Chatterjee et al. 2005, Stuhmer and Bargou 2006, Saha, Jiang et al. 2010, Saha, Jiang et al. 2010)

1.3 ***Proteasome inhibitors and 17p deletion***: Bortezomib as part of induction as well as maintenance therapy has been associated with improved outcomes in patients with *TP53* deletion. In a series of 354 MM patients treated within the HOVON-65/GMMG-HD4 trial, Neben et al analyzed the effect of a bortezomib-based treatment before and after autologous stem cell transplantation compared with standard treatment without bortezomib. Patients with del(17p13) had a significant benefit with the bortezomib-containing treatment: the median PFS was 12.0 months without bortezomib compared to 26.2 months (P = .024) with bortezomib; the 3 year-OS was 17% and 69%, respectively (P = .028).

1.4 ***Ixazomib***: MLN9708, which has been formulated for both intravenous (IV) and oral (PO) administration, is a small molecule proteasome inhibitor. It is the citrate ester of the biologically active boronic acid form, MLN2238. In water or aqueous systems, MLN9708 rapidly hydrolyzes to MLN2238, therefore all doses and concentrations are expressed as MLN2238. Nonclinical studies were conducted with a solution of either MLN2238 or MLN2238 in equilibrium with MLN9708. Similar to bortezomib, MLN2238 potently, reversibly, and selectively inhibits the 20S proteasome. However, in contrast to bortezomib, it has a shorter dissociation half-life (t1/2) that may contribute to increased tissue distribution. Bortezomib has a slowly reversible dissociation rate from the red blood cell proteasome, while MLN2238 demonstrates a more rapidly reversible dissociation rate from the blood but sustained effects on bone marrow and tumor proteasomes suggesting better tissue distribution. The pharmacologic implications of this difference in binding kinetics and tissue distribution may in turn result in differences in safety and efficacy profiles in a broader range

of tumors. In xenograft-bearing mice, the more rapid dissociation rate correlates with an increased ratio of tumor proteasome inhibition to blood proteasome inhibition, and ixazomib shows greater antitumor activity in several xenograft models, both solid tumor and bortezomib-resistant xenografts, than bortezomib.

Please refer to the latest version of the Ixazomib IB for further details.

Nonclinical Pharmacology: MLN2238 refers to the biologically active, boronic acid form of the drug substance, ixazomib citrate (MLN9708). Ixazomib citrate refers to the citrate ester of MLN2238. In water or aqueous systems, the equilibrium shifts from ixazomib to the biologically active boronic acid form MLN2238. All doses and concentrations are expressed as the boronic acid, MLN2238.

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 Cmax and $AUC_{0\text{-}24hr}$ after oral administration was low to moderate, similar to that after IV administration. The terminal $t_{1/2}$ after oral administration was also similar to that after IV administration. Comparison of the PK profiles after IV or PO administration in the dog is reported in further detail in the IB. MLN2238 is predicted to have very low CLb (0.0045 L/hr/kg) and a moderate Vss,b (0.79 L/kg) with a long terminal $t_{1/2}$ (>24 hours) in humans. The human efficacious IV dose of MLN2238 is predicted to be 2.0 mg/m^2 (0.054 mg/kg) twice weekly. The human efficacious oral dose is predicted to be between 2 and 5 mg/m^2 twice weekly, based on a predicted oral F of between 41% (as seen in rats) and 100% (as seen in dogs). The efficacious dose projection for once weekly oral would be higher than twice weekly oral (data not provided).

Metabolism appears to be a major route of elimination for MLN2238 and urinary excretion of the parent drug was negligible (<5% of dose). In vitro in liver microsomes, the metabolism of MLN2238 was high in mice and low to moderate in all other species studied. MLN2238 is metabolized by multiple cytochrome P450 (CYP) isozymes and non-CYP enzymes and proteins. The rank order of relative biotransformation activity of each of the 5 major human CYP isozymes in the in vivo studies was 3A4 (34.2%) >1A2 (30.7%) >2D6 (14.7%) >2C9 (12.1%) >2C19 (negligible).

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

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

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

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

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

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

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

<u>*In Vivo* Toxicology</u>: Details of the *in vivo* toxicology IV dosing and oral dosing studies are provided in the IB. To summarize, the toxicologic effects seen in the IV and PO studies are qualitatively similar to what was previously observed in rodents dosed with bortezomib. MLN2238 did not cause significant toxicities that have not been previously observed after dosing with bortezomib. Therefore, on the basis of the similarity in the toxicity profile in rats between MLN22338 and bortezomib, MLN2238 is not known to present any additional safety risks beyond those that occur after treatment with bortezomib. In addition, there were no significant findings at tolerated exposures in dogs observed after PO administration that were not seen after IV administration, and similar exposures were tolerated regardless of the route of administration.

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

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

- Lymphoid cell depletion that may be associated with increased risk of infection, including re-activation of herpes zoster.
- Acute phase response that may result in fever and metabolic changes.

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

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

Ixazomib has been evaluated as an oral single agent in phase 1 studies that have included patients with advanced solid tumors, lymphoma, relapse/refractory MM (RRMM), and relapsed or refractory light-chain (AL) amyloidosis and demonstrated early signs of activity. Ongoing studies continue to investigate both single-agent ixazomib and ixazomib in combination with standard treatments. Based on encouraging preliminary data observed in patients with MM requiring systemic treatment, two phase 3 trials in newly diagnosed MM (NDMM) (C16014) and RRMM (C16010) patient populations are currently evaluating ixazomib in combination with lenalidomide (Revlimid®) and dexamethasone (RevDex) versus placebo/RevDex. Both trials are combining ixazomib at a weekly dose of 4.0 mg on Days 1, 8, and 15 in a 28-day cycle to a standard dose of lenalidomide with a weekly dexamethasone dose of 40 mg. In addition, ongoing clinical pharmacology studies include evaluation of drug-drug interactions with ketoconazole and rifampin, effect of food, and oral bioavailability. Studies evaluating the safety and pharmacokinetic (PK) of ixazomib alone (in Japanese patients) and in combination with lenalidomide and dexamethasone in Asian adult patients (including Japanese patients) with a diagnosis of NDMM are ongoing.

As of 27 March 2013, preliminary clinical data are available for a total of 653 patients across 13 studies. The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with bortezomib though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation.

Fatigue was the most common AE reported among 384 patients treated in the oral (PO) studies (47%). Other common AEs reported in the pooled intravenous (IV) and PO safety populations include nausea, thrombocytopenia, diarrhea, and vomiting. Rash is also a commonly reported treatment-emergent event; however, there is some variety in its characterization and causality resulting in different preferred terms to describe it. A high-level term outline of rash events includes rashes, eruptions and exanthems NEC; pruritus NEC; erythemas; papulosquamous conditions; and exfoliative conditions. The dose escalation phases of most trials reported in the IB have now completed enrollment, and gastrointestinal (GI) symptoms were the common dose-limiting toxicities (DLTs) when the use of

prophylactic anti-emetics was not permitted per protocol. In the expansion cohorts or phase 2 cohorts (per each study), the incidence and severity of GI symptoms was mitigated by the use of the lower maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) (per each study) and standard clinical usage of anti-emetics and/or antidiarrheal medications as deemed appropriate. Prophylactic use of anti-emetics has not been required as with other agents but has been used according to standard practice and are effective.

The most frequent (at least 20%) treatment-emergent adverse events (TEAEs) reported with the PO formulation pooled from single-agent studies (n=201) irrespective of causality to ixazomib, include nausea (53%), fatigue (51%), diarrhea (44%), thrombocytopenia (34%), vomiting (38%), decreased appetite (32%), fever (21%), and anemia (21%). The most frequent (at least 20%) TEAEs reported with the PO formulation pooled from combination trials (irrespective of the combination) (n=173), irrespective of causality to ixazomib, include diarrhea (47%), fatigue (44%), nausea (38%), peripheral edema (35%), constipation (33%), insomnia (29%), thrombocytopenia (28%), anemia (26%), vomiting (26%), neutropenia (25%), back pain (24%), pyrexia (23%), fever (20%), cough (20%), hypokalemia (20%), neutropenia (20%), and upper respiratory tract infection (20%). Overall rash of all grades is reported in approximately 50% of patients and is more common when ixazomib is given in combination with lenalidomide, where rash is an overlapping toxicity. Additional detailed information regarding the clinical experience of ixazomib may be found in the IB, including information on the IV formulation.

Pharmacokinetics and Drug Metabolism: Clinical IV and PO PK data show that ixazomib citrate (measured as the biologically active boronic acid form of ixazomib [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral ixazomib citrate is rapidly absorbed with a median single-dose first time of occurrence of maximum (peak) concentration (Tmax) of approximately 0.5 to 2.0 hours and a terminal disposition half-life (t1/2) after multiple dosing of approximately 5 to 7 days. Results of a population PK analysis (n = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.(Gupta, Saleh et al. 2011, Gupta, Saleh et al. 2012) Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for ixazomib using the population PK analysis. Please refer to the current ixazomib IB and Safety Management Attachment (SMA) for information on the PK for IV doses of ixazomib.

Clinical Study C16009 (Arm 1) with ketoconazole, a strong CYP3A4 inhibitor, showed a 2-fold increase in area under the plasma concentration versus time curve (AUC) in the presence of ketoconazole. This resulted in the continued exclusion of strong CYP3A4 inhibitors in ongoing/planned clinical studies.

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

Table 1-1 Clinical Studies of Oral Ixazomib

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 60	PO, TW, single agent	0.24-2.23 mg/m^2 TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia Closed to enrollment
C16004 RRMM N = 60	PO, W, single agent	0.24-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea Closed to enrollment
C16005 NDMM N = 65	PO, W, combination with LenDex 28-day cycle	1.68-3.95 mg/m^2 W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D[a]: 4.0 mg fixed (switched to fixed dosing in phase 2, equivalent to 2.23mg/m^2) Closed to enrollment
C16006 NDMM N = 20	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with Melphalan and Prednisone	Arm A[a]: 3-3.7-mg fixed dose TW DLT: rash, thrombocytopenia, subileus Arm B[a]: 3-5.5-mg fixed dose, W DLT: Esophageal ulcer nausea, vomiting, hematemesis, thrombocytopenia, ileus, neurogenic bladder MTD = 3.0 mg
C16007 RRAL N = 27	PO, W, single agent	4-5.5-mg fixed dose[a] W DLT: thrombocytopenia, diarrhea, dyspnea, acute rise in creatinine, cardiac arrest MTD: 4.0 mg W
C16008 NDMM N = 64	PO, TW, combination with LenDex 21-day cycle	3.0-3.7-mg fixed dose[a] W MTD: 3.0 mg Closed to enrollment
C16009 Solid tumors, Lymphomas N = 54	PO, W, single agent	5.5-mg fixed dose[a] W
C16010 RRMM N = 200	PO, W, with LenDex versus placebo-LenDex	4.0 mg W
C16011 RRAL N = 4	PO, W, with Dex versus physician's choice of a Dex-based regimen	4.0 mg W
C16013 RRMM N = 9	PO, W, with LenDex	4.0 mg W

Table 1-1 Clinical Studies of Oral Ixazomib

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

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

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

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

1.5 ***Potential Risks of Ixazomib***:

The emerging safety profile indicates that ixazomib is generally well tolerated. The adverse events (AEs) are consistent with the class-based effects of proteasome inhibition and are similar to what has been previously reported with bortezomib, though the severity of some, for example peripheral neuropathy, is less. While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention, or, as needed, dose modification or discontinuation. In the four ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral ixazomib in patients with differing malignancies (multiple myeloma, AL amyloidosis, non-hematologic cancers, and lymphoma), a total of 201 patients have been treated as of 27 March 2013. These patients

have been treated with different doses of ixazomib, as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral ixazomib studies (C16003, C16004, C16007, and C16009) are shown in Table 1-2.

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

Primary System Organ Class Preferred Term	Oral Single Agent Total n=201 (n%)
Subjects with at Least One Adverse Event	197 (98)
Gastrointestinal disorders	160 (80)
Nausea	106 (53)
Diarrhea	88 (44)
Vomiting	77 (38)
Constipation	46 (23)
Abdominal pain	33 (16)
General disorders and administration site conditions	151 (75)
Fatigue	103 (51)
Pyrexia	51 (25)
Edema peripheral	27 (13)
Asthenia	31 (15)
Nervous system disorders	92 (46)
Headache	29 (14)
Dizziness	26 (13)
Neuropathy peripheral	21 (10)
Metabolism and nutrition disorders	107 (53)
Decreased appetite	64 (32)
Dehydration	37 (18)
Blood and lymphatic system disorders	98 (49)
Thrombocytopenia	68 (34)
Anemia	42 (21)
Neutropenia	29 (14)
Lymphopenia	20 (10)
Skin and subcutaneous tissue disorders	90 (45)
Rash macular[a]	23 (11)
Musculoskeletal and connective tissue disorders	93 (46)
Back pain	24 (12)
Arthralgia	28 (14)
Respiratory, thoracic and mediastinal disorders	78 (39)
Cough	28 (14)
Dyspnea	30 (15)
Infections and infestations	89 (44)
Upper respiratory tract infection	31 (15)

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

Primary System Organ Class Preferred Term	Oral Single Agent Total n=201 (n%)

Source: Ixazomib Investigator's Brochure Edition 7
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0
Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.
a Note that rash maculopapular and rash macular represent the two most common terms used to describe rash.

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

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

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 (n%)
Subjects with at Least One Adverse Event	163 (94)
Gastrointestinal disorders	139 (80)
Nausea	65 (38)
Diarrhea	81 (47)
Vomiting	51 (29)
Constipation	57 (33)
General disorders and administration site conditions	132 (76)
Fatigue	76 (44)
Pyrexia	39 (23)
Edema peripheral	61 (35)
Asthenia	20 (12)
Nervous system disorders	115 (66)

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

Primary System Organ Class Preferred Term	Total Oral Combo Agent (5/6/8/13) n = 173 (n%)
Headache	28 (16)
Dizziness	34 (20)
Neuropathy peripheral	45 (26)
Metabolism and nutrition disorders	91 (53)
Decreased appetite	25 (14)
Hypokalemia	34 (20)
Blood and lymphatic system disorders	88 (51)
Thrombocytopenia	49 (28)
Anemia	45 (26)
Neutropenia	43 (25)
Lymphopenia	20 (12)
Skin and subcutaneous tissue disorders	102 (59)
Rash maculopapular	29 (17)
Rash macular[a]	22 (13)
Musculoskeletal and connective tissue disorders	99 (57)
Back pain	42 (24)
Pain in extremity	31 (18)
Arthralgia	22 (13)
Respiratory, thoracic and mediastinal disorders	80 (46)
Cough	36 (21)
Dyspnea	26 (15)

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

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

Source: Ixazomib Investigator's Brochure Edition 7
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, version 15.0
Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.
Data from ongoing blinded pivotal trials (C16010) are not included.
a Note that rash maculopapular and rash macular represent the two most common terms used to describe rash

The clinical experience with ixazomib also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent ixazomib, when combined with established therapies, and across the malignancies studied (advanced solid tumors, non-Hodgkin's disease, Hodgkin's disease, relapsed and/or refractory multiple myeloma, relapsed or refractory systemic light chain amyloidosis, and newly diagnosed multiple myeloma) to date.(Kumar, Bensinger et al. 2014, Kumar, Bensinger et al. 2014, Kumar, Berdeja et al. 2014, Richardson, Baz et al. 2014)

1.6 **Idasanutlin (RO5503781)**: Idasanutlin is a potent and selective inhibitor of the p53-MDM2 interaction that activates the p53 pathway and induces cell cycle arrest and/or apoptosis in a variety of tumor types expressing wild-type p53 in vitro and in vivo. It binds MDM2 in the p53 pocket with a high affinity (K_D=11 nM) leading to stabilization and accumulation of p53 and consequent signaling. It blocks cell cycle progression in G1 and G2 leading to inhibition of cancer cell growth. It has a 30-fold selective toxicity for wild-type vs. mutant p53 cells. In a recent Phase 1 trial, treatment with idasanutlin was well tolerated and efficacy was seen in some patients with acute myeloid leukemia. Additionally, preclinical models have established that the activity of idasanutlin may be potentiated when combined with rational therapeutic partners to improve efficacy, lending credence to such combinational regimens displaying synergistic anti-cancer effects.

Non-clinical Pharmacology: The pharmacology, pharmacokinetics, and toxicology of idasanutlin have been investigated in several nonclinical studies. In cell-free assays, idasanutlin binds to MDM2 protein with high affinity (dissociation constant [K_D] = 5.7 nM) and inhibits MDM2-p53 binding with drug concentration, which causes IC_{50} of 6.6 ± 1.0 nM. Exposure of cultured cancer cells to the compound leads to a dose-dependent accumulation of p53 protein and activation of its transcriptional targets and the p53 pathway. As a result, cancer cells undergo a cell cycle block in the G1 and G2 phase followed by apoptosis. In

vivo, idasanutlin has shown antitumor activity at nontoxic doses against an established osteosarcoma xenograft model. These nonclinical pharmacology results support further evaluation of idasanutlin in clinical studies.

Nonclinical Pharmacokinetics and Metabolism: Single-dose pharmacokinetics of idasanutlin were evaluated in mice, rats, dogs, and monkeys following intravenous (IV) and oral dosing. High exposures were achieved in all nonclinical species after oral administration and high oral bioavailability was observed in rodents (low in non-rodents). Multiple-dose pharmacokinetics of idasanutlin were studied during general toxicology studies in Han Wistar rats and cynomolgus monkeys following oral dosing. Exposure increased with increasing dose level and no gender difference was apparent. In rats, there was generally no accumulation or loss of exposure after multiple days of dosing. However, after repeat dosing of idasanutlin in monkeys, decreases in exposure were apparent at all dose levels, which correlates to monkey-specific CYP3A induction in intestine and liver.

In vitro plasma protein binding was high (99.99%) and similar across species (mouse, rat, dog, monkey, and human). Tissue distribution studies in rats showed that idasanutlin was widely distributed and the highest concentration was observed about 4 hours post dose in intestine, liver, adrenal gland, colon, cecum, kidney cortex, and gastric mucosa. Low metabolism occurred in rat, monkey, and human liver microsomal and hepatocyte incubations. Based on in vitro results, both rats and monkeys produced the same metabolites as humans, which supported the choice of these species for toxicological evaluation. In rats in vivo, [^{14}C]-idasanutlin and its related metabolites were mainly excreted hepatically through bile with minimal renal elimination. Results from in vivo metabolic profiles and metabolite identification of idasanutlin in human plasma and urine showed that 1) glucuronidation of idasanutlin seems to play a minor role in terms of human plasma exposure; 2) rat and cynomolgus monkey metabolic patterns together cover the human plasma metabolite pattern; and 3) idasanutlin is not excreted through urine.

At therapeutic dose levels, idasanutlin has the potential for drug-drug interactions as a perpetrator with CYP2C8 substrates. Idasanutlin is metabolized by multiple metabolic enzymes, mainly by CYP2C8, CYP3A4/5, and UDP-glucuronosyltransferase (UGT). Strong inhibitors and/or inducers of these enzymes may affect exposure of idasanutlin.

Toxicology and Safety Pharmacology

Pivotal repeat-dose cycling studies in rats and monkeys that consisted of two dosing cycles of 10 days duration with an intervening drug holiday of 18 days, followed by a recovery period, confirmed that idasanutlin produced target organ toxicity that was expected for a compound that disrupts the cell cycle. Safety findings identified in the toxicology studies at exposures that approximate the anticipated therapeutic range are considered clinically manageable (e.g., diarrhea), monitorable (e.g., suppression of blood cell components) and/or reversible (e.g., body and organ weight changes and diarrhea). In the Good Laboratory Practice (GLP) cycling studies, oral administration of idasanutlin to rats and monkeys resulted in moribundity; diarrhea (monkeys only); decreased body weight and/or body weight gain (rats only); decreased food consumption; sporadic increases in serum liver function tests (rats only); and target organ toxicities, including bone marrow hypocellularity, reduced leukocytes, erythrocytes, and/or platelets, decreased thymus or spleen weights, and lymphoid depletion in the thymus, spleen, mesenteric lymph nodes, and/or gut-associated lymphoid tissue (GALT). Moribundity in monkeys occurred at doses ≥ 60 mg/kg/day. In rats, moribundity and premature death were noted at doses ≥ 500 mg/kg/day. In general, treatment-related findings either fully or partially resolved during the recovery period. The maximum tolerated doses

(MTD) for two cycles of treatment with idasanutlin were considered to be 30 and 300 mg/kg/day in cynomolgus monkeys and Wistar rats, respectively. No biologically relevant adverse effects were observed in the CNS or pulmonary system. Cardiovascular effects were limited to a reversible increase in heart rate in male monkeys at doses above the MTD. A GLP human ether-à-go-go-related gene (hERG) assay conducted at physiological temperature showed an IC_{20} of ≥ 1.8 μM, but was of limited value because of insolubility of idasanutlin. Importantly, there was no effect on the corrected QT interval (QTc) in the pivotal monkey study at doses that exceeded the MTD. Based on ultraviolet A (UVA)/ultraviolet B (UVB) absorption spectrum, idasanutlin demonstrates a potential for phototoxicity. Therefore, an in vivo phototoxicity study was conducted in Long Evans rats. Idasanutlin did not induce a phototoxic skin reaction at any dose, which indicated that there is little to no risk of phototoxicity in cancer patients.

RO0478485 (4-amino-3-methoxy-benzoic acid) is a potential impurity and degradation product of idasanutlin that is formed by hydrolysis of the amide bond. RO0478485 induced a weak but dose-related increase in the number of revertant colonies after metabolic activation. In order to reduce the amount of this impurity to levels as low as reasonably possible, adjustments to the drug substance and drug product process and different storage conditions are under evaluation.

CLINICAL INFORMATION

Two Phase I clinical studies of idasanutlin are complete in patients with solid tumors (Studies NP27872 and NP28902) and one Phase I/Ib study is currently ongoing in patients with AML (Study NP28679).

Table 1-4 Completed, Ongoing, and Planned Idasanutlin Studies

Protocol No.	Phase, Design	Patient Population, No. of Patients	Monotherapy/ Combination Therapy	Formulation	Current Status
NP28679	Phase I/Ib, Dose-escalation of single agent (Part 1) and in combination with cytarabine (Part 2) or in combination with cytarabine and anthracycline (Part 3), and assessment of PK and safety of optimized SDP formulation (Part 4)	AML, N = 105 [a] (Part 1, N = 20 Part 1 extension, N = 9 Part 2, N = 23 Part 2 extension, N = 38 Part 3, N = 0 Part 4, N = 15)	Idasanutlin monotherapy and combination therapy with cytarabine - containing regimens	Parts 1, 2, 1 extension, 2 extension = MBP Part 4 = SDP	Part 1 and Part 2 dose escalation complete; Part 1 extension discontinued [b], Part 2 extension complete, no patients enrolled in Part 3 [c], Part 4 is ongoing [d]
NP27872	Phase I, Dose-escalation, food-effect, and biomarker study	Solid tumor, N = 99 (Dose escalation, N = 48 Biomarker cohorts, N = 37 Food-effect, N = 10 Apoptosis, N = 4)	Idasanutlin monotherapy	MBP	Completed;
NP28902	Phase I, DDI with a strong CYP3A4 inhibitor (Part 1), new formulations rBA (Part 2), and food-effect of optimized SDP formulation (Part 3)	Solid tumor, N = 61 (DDI Part 1, N = 20 [f] rBA Part 2, N = 12 [f] Part 3, N = 29 [g] Optional treatment extension, N = 20 [f,h])	Idasanutlin monotherapy	Part 1 Part 2 = optimized MBP, initial SDP, SDP Part 3 = SDP	Enrollment is complete.
WO29519	Phase III, multicenter, double-blind, randomized, placebo-controlled study of idasanutlin in combination with cytarabine compared with cytarabine plus placebo	Relapsed/refractory AML, N = 440	Idasanutlin in combination with cytarabine	SDP	Protocol in preparation

AML = acute myeloid leukemia; DDI = drug-drug interactions; IV = intravenous; MBP = micro-precipitated bulk powder; PK = pharmacokinetic; rBA = relative bioavailability; SDP = spray-dried bulk powder.

[a] Data snapshot date, 26 February 2015.

[b] Extension discontinued due to benefit (complete remission) not reaching sufficiently high levels to continue monotherapy development in this high-risk population.

[c] Planned enrollment, approximately 15–20 patients.

[d] Planned enrollment, approximately 12–18 patients.

[f] As of the data snapshot date of 14 February 2014, a total of 9 patients were enrolled in the extension.

[g] [h] Patients from the optional extension had previously participated in Part 1, 2 or 3.

The first-in-human study, NP27872, is a multicenter, open-label, Phase I, dose-escalation study of single agent idasanutlin administered orally to patients with advanced malignancies except leukemia. 99 patients were enrolled in the study: a total of 37 patients have been enrolled into biomarker cohorts in order to gain preliminary information on prognostic, pharmacodynamic, and early response biomarkers and clinical efficacy at or below the MTD in preparation for Phase II clinical development (results not yet available). In addition, evaluation of the effect of food on the pharmacokinetic (PK) parameters of idasanutlin was conducted in a subgroup of 10 patients enrolled in Study NP27872.
Study NP28902 is a multicenter, open label, crossover design, clinical pharmacology study to investigate idasanutlin with drug-drug interaction with posaconazole (Part 1, 20 patients) and relative bioavailability of new formulations of idasanutlin (Part 2, 12 patients), and food-effect on the pharmacokinetics of a single dose with the optimized SDP formulation (Part 3, 29 patients, not included in the data cut-off) in patients with solid tumors. A total of 61 patients were enrolled and enrollment is closed. Twenty of the 61 patients continued into the optional treatment extension following completion of clinical pharmacology assessments. Nine of these twenty patients are included in the data cut-off.

Study NP28679 is a multicenter, open-label Phase I/Ib study of idasanutlin in escalating doses as a single agent (Part 1); in combination with cytarabine (Part 2); or in combination with cytarabine and anthracycline (Part 3) in patients with AML, and to characterize the PK and safety profiles of the optimized SDP formulation at the recommended Phase II dose in combination with cytarabine (Part 4). The first patient received idasanutlin on 21 February 2013. The study is ongoing and enrollment is expected to be completed in 2015.
As of 25 February 2015, 105 patients have been enrolled in the study (29 in Part 1 [20 in dose escalation and 9 in extension] and 61 in Part 2 [23 in dose escalation and 38 in extension]. Dose escalation is now complete and enrollment closed in Part 1, Part 2 and their respective extension arms. Enrollment for Part 3 and 4 is ongoing and at time of clinical cut off, no patients were enrolled in Part 3 and 15 patients were enrolled in Part 4.

Clinical Pharmacokinetics
The half-life of idasanutlin was approximately 1 day. There was apparent dose-proportionality for last-day (3, 5, or 15 depending on schedule) area under the curve (AUC) up to 2400 mg/day with ~ 50% inter-patient variability in patients with solid tumors (NP27872 data). No apparent difference in PK exposure was found between patients with solid tumors (Study NP27872) and patients with AML (Study NP28679) in the dose range of 400 to 1600 mg daily × 5 days. Although there was a small sample size (N = 13), PK data from East Asian patients did not appear to differ from other patient ethnicities (mainly Caucasians). Age does not appear to have an impact on PK exposure. A drug-drug interaction study with posaconazole as a strong CYP3A4 inhibitor was conducted in 20 (18 evaluable)

patients with solid tumors. No change in maximum plasma concentration (Cmax) and modestly higher (32%) change in AUC were found with CYP3A4 inhibition with minimal increase (22% in Cmax and 23% in AUC) with simulated steady−state profiles. Since a strong CYP3A4 inhibitor was chosen for the study, all CYP3A4 inhibition risks are deemed negligible.

Evaluable PK data are available for 12 patients in Part 2 (relative bioavailability) of Study NP28902 administered 400 mg reference MBP (micro-precipitated bulk powder), an improved 400 mg MBP, and a 400 mg SDP (spray-dried powder) formulations in randomized sequence on Days 1, 8, or 15 under fasting conditions. Overall, preliminary clinical PK results indicate that: idasanutlin exposure, based on AUC to the last measurable time point (AUC168h) and Cmax, was higher with the SDP formulation (42% and 47%, respectively) than the previous (reference) MBP formulation. The SDP will be the formulation in future trials including the current study. Part 3 of this study examined food-effect of a high energy/high-fat meal (1000 kcal with 50% from fat) and low-fat meal (500 kcal with 30% from fat) on PK. In 19 evaluable patients (receiving 3 crossover treatments) no evidence for a food-effect was demonstrated.Equivalence in all PK exposure parameters analyzed (90% confidence interval (CI)) was shown, while the low-fat meal demonstrated less than 20% increase in all PK exposure parameters, just outside the upper limit of 90% CI for bioequivalence.

Clinical Pharmacodynamics
Macrophage inhibitory cytokine ([MIC-1], a secreted protein that is strongly induced by activated p53) serum levels, has been used to assess pharmacodynamic effects in Study NP27872. Analysis of patients treated with 100 to 3200 mg/day of idasanutlin showed that the minimum level for p53 induction occurred at the lowest tested dose of 100 mg/day or a corresponding plasma level of 500 ng/mL of idasanutlin. There was no upper limit with the dose tested. However, a comparison of MIC-1 elevation between the idasanutlin dosing schedules demonstrated poor ability to activate p53 with the weekly schedule.

Preliminary analysis of PK and safety data showed that there is an apparent pharmacokinetic / pharmacodynamic relationship between an AUC per cycle and Cycle 1 platelet nadir; this was mostly associated with the daily (× 5 days or × 3 days) dosing schedules; no correlation exists for the weekly schedule. No correlation was apparent between idasanutlin plasma concentration and QT corrected using Fridericia's method (QTcF) for both solid tumor and AML patient populations, which suggests there was no apparent QT prolongation signal.

Optimal Schedule
Idasanutlin PK exposure, pharmacodynamic effects (e.g., MIC-1, as a p53 activation marker), and target-mediated hematological changes (platelet reduction in particular) were evaluated to support the optimal dosing schedule. A comparison of MIC-1 elevation between the idasanutlin dosing schedules demonstrated poor ability to activate p53 with the weekly schedule. The daily × 3 days dose regimen did not achieve steady-state exposure, achieved a shorter period of SD, and did not alleviate thrombocytopenia. Therefore, the daily × 5 days schedule is proposed as optimal for future clinical trials including the current study.

Clinical Efficacy
No relapsed solid tumor patients achieved a monotherapy response to idasanutlin, according to Response Evaluation Criteria in Solid Tumors (RECIST) in Study NP27872. Twenty-six (31%) patients had stable disease and remained on study an average of 64 days. Analysis in tumor tissues of PD biomarkers associated with the p53 pathway showed significant changes

upon dosing for most biomarkers in those patients having paired biopsies. These findings confirmed the proposed mechanism of action of idasanutlin activating the p53 pathway through MDM2 antagonism.

Evaluable hematological malignancy response assessments from the NP28679 study were available for patients in Part 1, Part 1 EXT, Part 2, Part 2 EXT and Part 4 arms at time of clinical data cutoff date 25 February 2015. Response assessments were noted as follows:

Part 1: Twenty (20) patients received monotherapy idasanutlin during Part 1 dose escalation at 400 mg (n = 2), 800 mg (n = 6) and 1600 mg (n = 12) daily x 5 days. Five (5) patients achieved marrow clearance on biopsy, Complete Remission/Complete Remission without platelet recovery (CR/CRp) [n=2] or Complete Remission with insufficient recovery of peripheral counts (CRi)/Morphologic Leukemia Free State (MLFS) [n=3].

Part 1 Extension: Nine (9) patients received monotherapy idasanutlin at 600 mg two times per day (BID) X 5 days. Best responses reported for the 8 evaluable patients were 2 CRi/MLFS, 2 Hematologic Improvement (HI) and 4 Progression of Disease (PD).

Part 2: Twenty-three (23) patients were enrolled in Part 2 dose escalation (idasanutlin and cytarabine) at daily doses of 400 mg (n = 10, with 1 ineligible patient), 800 mg (n =7), and 1200 mg (n =6). Six (6) relapsed AML patients achieved CR/CRp.

Part 2 Extension: Thirty-eight patients (38) with relapsed/refractory AML were enrolled to Part 2 extension randomized to idasanutlin 600 mg BID with (n=21) or without cytarabine (n=17). Thirty-three (33) patients have responses reported with 6 CR/CRps (5 in combination, 1 with idasanutlin monotherapy), 1 Partial Response (PR) [defined as >50% decrease in bone marrow blasts] (combination), 3 HI (monotherapy), 23 PD (13 with monotherapy and 10 with combination).

Part 4: Fifteen patients (15) have enrolled in the Part 4 bridging arm with the SDP formulation in combination with cytarabine 1g/m2 x 6d as of 25 February 2015. Fourteen (14) patients have responses reported, with 4 CR/CRp, 1 PR, 2 HI, and 7 PD.

Table 1-5 Summary of Best Hematologic Malignancy Response over the Duration of Treatment-Study NP28679

	Part 1 Dose Escalation idasanutlin (MBP) Monotherapy	Part 1 Extension idasanutlin (MBP) Monotherapy	Part 2 Dose Escalation idasanutlin (MBP) plus Cytarabine	Part 2 Extension idasanutlin (MBP) Monotherapy	Part 2 Extension idasanutlin (MBP) plus Cytarabine	Part 4 idasanutlin (SDP) plus Cytarabine
Enrolled	20	9	23	17	21	15
Evaluable	17	8	22 [a]	17	16	14
CR/CRp	2	0	6	1	5	4
CRi/MLFS	3	2	1	0	0	0
PR	3	0	2	0	1	1
HI	4	2	2	3	0	2
PD	5	4	10	13	10	7
Missing	0	0	1	0	0	0

CR = complete remission; CRi/MLFS = complete remission with incomplete recovery of peripheral counts/morphological leukemia-free state; CRp = complete remission with incomplete platelet recovery; HI = hematological improvement; PD = progressive disease; PR = partial response.

[a] 1 patient did not have AML and was not evaluable.

Clinical Safety

In solid tumor studies of idasanutlin, consistent with the mechanism of action, p53 induction caused "on-target" toxicity in hematopoietic cells. Higher exposures led to adverse events of neutropenia and thrombocytopenia, which while reversible could reach grade 3/4 in some patients. Modeling of this toxicity demonstrated that cytopenias were exposure dependent, with delayed nadirs in blood counts. Recovery at higher exposures caused delays in subsequent cycles of therapy, which was alleviated by dose-reduction for subsequent cycles.

- Most common AEs were diarrhea, nausea, vomiting, decreased appetite, and thrombocytopenia.
- Most common severe AEs of NCI-CTC Grade 3 were thrombocytopenia, neutropenia, anemia, nausea, and diarrhea.
- Most common SAEs were thrombocytopenia, febrile neutropenia, neutropenia, leukopenia, and anemia.
- Seven (7) deaths occurred during the study, 5 due to progressive disease, and 2 due to fatal AEs (intra-abdominal hemorrhage, pulmonary embolism)

Overall, the current safety profile of Study NP28679 in AML is consistent with findings from other studies of relapsed/refractory AML patients treated with cytarabine. For those patients receiving cytarabine with idasanutlin, there is a similarity of the safety profiles for the two agents. Specifically, they both may manifest AEs for gastrointestinal disorders, myelosuppression, febrile neutropenia, infection including pneumonia, or cellulitis. When both agents are given concurrently, it may not be possible to distinguish whether the IMP or the disease, if not both, may have contributed to the onset of a given AE.

At the data cutoff date of 14 February 2014 for Study NP28902 and with final data for Study NP27872, 131 patients with advanced malignancies (excluding leukemia) had received idasanutlin. In the Phase I entry-into-human dose escalation study NP27872 there are 99 patients with available data and the Phase I drug-drug interaction/relative bioavailability study NP28902 comprised 32 patients. All patients in both studies experienced at least one adverse event, and 32 of 99 patients in Study NP27872 and 5 of 32 patients in Study NP28902 experienced at least one serious adverse event. Of these 32 patients in Study NP27872, 25 experienced serious adverse events that were considered by the investigator to be possibly, probably, or remotely related to study treatment, almost all of which were related to hematopoietic or gastrointestinal toxicities. Of the 5 patients who reported an SAE in Study NP28902, only 1 patient experienced a serious adverse event of thrombocytopenia (Grade 4) considered by the investigator to be related to study treatment. A total of 18 patients in Study NP27872 and 3 patients in Study NP28902 Part 1 (idasanutlin+posaconazole) experienced adverse events that led to withdrawal from study treatment.

The most frequently affected system organ classes (SOC; 10% of all patients) in Study NP27872 were gastrointestinal disorders (97/99 [98.0%]), general disorders and administration site conditions (74/99 [74.7%]), metabolism and nutrition disorders (63/99 [63.6%]), blood and lymphatic disorders (50/99 [50.5%]), nervous system disorders (48/99 [48.5%]), musculoskeletal and connective tissue disorders (45/99 [45.5%]), respiratory,

thoracic and mediastinal disorders (44/99 [44.4%]), infections and infestations (24/99 [24.2%]), skin and subcutaneous tissue disorders (20/99 [20.2%]), investigations (19/99 [19.2%]), psychiatric disorders and vascular disorders (13/99 [13.1%] each), and injury, poisoning, and procedural complications (10/99 [10.1%]) ([CD]). A summary of the most frequent AEs occurring in at least 10% of the patients in any treatment group is shown in Table 1-6. The five most frequent AEs of any grade were diarrhea (74/99 [74.7%]), nausea (71/99 [71.7%]), vomiting (51/99 [51.5%]), decreased appetite (47/99 [47.5%]), and thrombocytopenia (39/99 [39.4%]).

Overall, two deaths in Study NP28902 and seven deaths in Study NP27872 were reported. In Study NP27872, five deaths were attributed to disease progression, and one death each to intra-abdominal hemorrhage and pulmonary embolism (unrelated) and pulmonary embolism (possibly related). In Study NP28902 the cause of death for 1 patient was attributed to disease progression and one patient died from unrelated aspiration pneumonia.

Table 1-6. Summary of Adverse Events with an Incidence Rate of at Least 10% Study NP28902

Total number of patients with at least one adverse event	20 (100.0%)
Total number of events	57
Diarrhea	12 (60.0%)
Nausea	10 (50.0%)
Vomiting	4 (20.0%)
Abdominal pain	1 (5.0%)
Fatigue	4 (20.0%)
Dehydration	3 (15.0%)
Abdominal distension	1 (5.0%)
Decreased appetite	2 (10.0%)
Hypomagnesaemia	1 (5.0%)
Constipation	2 (10.0%)
Dyspnea	1 (5.0%)
Asthenia	1 (5.0%)
Chest pain	1 (5.0%)
Early satiety	1 (5.0%)

Consistent with other ongoing studies of RO5503781, gastrointestinal (GI) adverse events (AEs) including nausea, vomiting, and diarrhea were common (diarrhea reported by >90%), but manageable in the NP28679 study (per clinical cutoff date 25 February 2015) both as monotherapy and in combination with Cytarabine in AML patients. Other frequently reported AEs were infection related (78%). The maximum tolerated dose (MTD), as defined in Protocol NP28679, was not reached.

Early deaths related to AML progression and infection was seen, as expected in the relapsed/refractory AML population.

1.7 Rationale for the current trial: In this trial we propose to evaluate the combination of ixazomib, an oral proteasome inhibitor, and idasanutlin, a p53 activator and dexamethasone in patients with 17p deleted MM. The approach is based on several hypotheses and available evidence.

- Patients with *TP53* deletion develop resistance very fast and remain the biggest stumbling block for successful control of this disease. Activating p53 will restore the sensitivity of the cell to current therapeutics and the combination is hence able to overcome drug resistance. This would be expected to be pronounced in cases where the remaining allele is of WT status, but not necessarily restricted to such.
- Ixazomib has excellent activity in myeloma, relapsed and newly diagnosed, and offers the possibility of an all-oral regimen for 17p-deleted myeloma. In addition, Ixazomib has excellent soft tissue penetration and may be particularly helpful in patients with 17p-deleted myeloma, who often have extramedullary disease. Addition of dexamethasone enhances the activity of Ixazomib and hence will be added as part of the regimen.

2.0 Objectives

2.1 Primary

2.11 Phase 1: The primary objective of the Phase 1 portion is to determine the maximum tolerated doses (MTD) of idasanutlin and ixazomib to be used in combination with dexamethasone in patients with relapsed or refractory multiple myeloma with TP53 (17p) deletion.

2.12 Phase 2: To evaluate the confirmed response rate of ixazomib and idasanutlin used in combination with dexamethasone in patients with relapsed or refractory multiple myeloma with TP53 (17p) deletion.

2.2 Secondary

2.21 Phase 1: To describe the toxicities and the confirmed response rate associated with the combination of idasanutlin, ixazomib and dexamethasone

2.22 Phase 2:

2.221 To describe the toxicities associated with the combination of idasanutlin, ixazomib and dexamethasone

2.222 To describe the CR and VGPR rates

2.223 To assess progression-free and overall survival

2.3 Exploratory

2.31 Assess mdm2 inhibition in bone marrow plasma cells

2.32 Identify potential biomarkers associated with response.

2.33 To explore the pharmacodynamic effects of idasanutlin.

3.0 Patient Eligibility

Enrollment open to Phase II as of Addendum 4

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Diagnosis of MM with deletion 17p (del17p) or monosomy 17 by FISH who have received at least one line of therapy.

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

- Calculated creatinine clearance (using Cockcroft-Gault equation below*) ≥30 mL/min
- AST (SGOT) and ALT (SGPT) ≤3.0 x upper limit of normal (ULN)
- Total bilirubin ≤1.5 × the upper limit of the normal range (ULN)
- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥75,000/mm^3
- Hemoglobin ≥8.0 g/dL

NOTE: White blood count and platelet count criteria must be met without any transfusion or growth factor support.

*Cockcroft-Gault Equation:

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

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

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

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

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

3.16 Ability to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use protected health information.

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

3.18 Willing to follow strict birth control measures as suggested below.

a) Female patients: If they are of childbearing potential (except if postmenopausal for at least 1 year before the screening visit, OR Are surgically sterile), agree to one of the following:
   - Practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through 90 days after the last dose of study drug, 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.)

b) Male patients: even if surgically sterilized (ie, status post-vasectomy), must agree to one of the following:
- Agree to practice effective barrier contraception during the entire study treatment period and through 90 days after the last dose of study drug, OR
- Agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable methods of contraception.)

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

3.19b Willing to provide bone marrow and blood samples for correlative research purposes (see Sections 6.2 and 14.1*).*

3.2 Exclusion Criteria

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

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

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

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

3.25 Major surgery ≤14 days before study registration.

3.26 All CYP2C8 inhibitors, inducers, and substrates should be discontinued ≥7 days prior to registration. Systemic treatment with CYP2C8 inhibitors (anastrozole, montelukast, quercetin, trimethoprim, gemfibrozil, rosiglitazone, pioglitazone), inducers (carbamazepine, phenytoin, rifabutin, rifampin), or substrates (amiodarone, repaglinide, rosiglitazone, sorafenib, torsemide) should be discontinued ≥7 days prior to registration.

3.27 Systemic treatment with strong inhibitors of CYP3A4 (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A4 inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, Gingko biloba, St. John’s wort) are not allowed ≤14 days before registration.

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

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

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

3.29b Known human immunodeficiency virus (HIV) positive.

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

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

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

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

3.29g Diarrhea >Grade 1, based on the NCI CTCAE grading, or currently taking antidiarrheals.

3.29h Need for ongoing therapeutic anticoagulation.

3.29i Female patients who are lactating or have a positive serum pregnancy test during the screening period.

3.29j Patients that have previously been treated with ixazomib, or who participated in a blinded study with ixazomib (whether treated with ixazomib or not).

4.0 Study Calendar

4.1 Test Schedule

Assessment	Screen	Cycle 1					Every Cycle				End of treatment and 30 day safety follow-up[15]
Day	**-14 to -1**	**1**	**6**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	
Window (days)					**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±7**
Medical/treatment history[1]	X										
Physical exam, ECOG performance status[2]	X	(X)[3]					(X)				X
Height (baseline only), weight, BSA	X	X[3]					X				X
Urinalysis	X										X
Hematology[3,5]	X	X[3]	X		X	X	X	(X)	(X)	(X)	X
Serum chemistry[3,4]	X	X[3]			(X)		X		(X)		X
Pregnancy test[6]	X						(X)				X
ECG[7], CXR	X										
Research blood and tissue assessments											
Correlative labs (See Section 14.0 for schedule)	X[8]	X[8]	X[8]				X[8]			X[8]	X[8]
Disease assessment											
Myeloma specific lab evaluations[9]	X	X[3]					X				X
BM aspirate/biopsy, cytogenetics, FISH[8,10]	X[8,10]									X[8,10]	X
Extramedullary disease[11]	X						X				X
Skeletal Survey[12]	X										
Response Assessment (See Section 11)							X				X
Study Drug Administration (See Section 7)											
Patient Medication Diary (see Appendix II)[13]											
Adverse events/toxicity evaluation (continuous)[14]	X		X				X				X
Concomitant therapy	X	X[3]	X		X	X	X				X

Cycle = 28 days

An (X) located within parentheses denotes investigator discretion with respect to tests and procedures.

Footnotes for Test Schedule

1. Myeloma/treatment history: Includes date of initial diagnosis, stage and extent of the disease at study entry and previous anti-tumor therapy (including surgical, radiation and systemic therapy).
2. Physical Examination: Consists of examination of major body systems including neurologic, digestive, respiratory, any evaluable sites of extramedullary myeloma, ECOG performance status (Appendix I).
3. For Day 1 of Cycle 1, screening results may be used if obtained within 3 days of treatment start
4. Full serum chemistry panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose [fasting at baseline], uric acid, calcium, phosphorus, magnesium, total bilirubin, alkaline phosphatase, ALT, AST, and LDH) will be obtained at screening and on Day 1 of Cycle 1 and 2 and an abbreviated

chemistry panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose and uric acid) on Day 15 for Cycle 1 and 2 only. Thereafter, a full chemistry panel will be collected on or within 3 days prior to Day 1 of all subsequent cycles and at the end of treatment visit/safety follow-up visit. Results must be reviewed before dosing on Day 1 of any given cycle.

5. Hematology (CBC including hemoglobin, hematocrit, WBC with complete differential, platelets) weekly for Cycle 1 and 2 only; for Cycles 3-6, hematology will be performed on Days 1 and 15. From Cycle 7 onwards, hematology will be performed on Day 1 only. Results must be available for review by the investigator before initiation of treatment.
6. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Initial pregnancy test is required ≤7 days prior to registration.
7. EKG (ECG) and CXR: Results may be used if obtained ≤30 days prior to registration.
8. Correlative Studies: bone marrow aspirate to be collected at study entry, end of Cycle 4, at suspected CR and PD; peripheral blood to be collected C1D1 pre-dose; C1D1 6 hours post-dose; C1D6; C2D1 6 hours post-dose and at PD.
9. Myeloma specific lab evaluations refers to: β2 Microglobulin, serum and 24-hour urine immunoelectrophoresis, serum immunoglobulin assay, Serum/urine immunofixation and serum free light chain with kappa/lambda ratio. (All are done at baseline; specific tests for subsequent cycles will be according to Section 11.2.)
10. Bone marrow aspirate and biopsy - quantify % myeloma cell involvement; bone marrow sample for cytogenetics and fluorescent in situ hybridization (FISH). Repeat bone marrow biopsy/aspirate if CR or sCR is suspected and as appropriate to confirm achievement of response. Bone marrow aspirate and blood to be collected for correlative studies at study entry, end of Cycle 4, at suspected CR and PD.
11. Extramedullary Disease: Assess by physical exam and/or radiologic evaluation at baseline and as clinically indicated. Disease that can be assessed by physical exam should be evaluated on Day 1 of each cycle. Disease that can be assessed by radiologic evaluation should be assessed according the IMWG criteria for evaluation of response. This may include computerized tomography (CT) scan, ultrasound, positron emission tomography [PET]/CT or MRI. The same method of assessment should be used at each evaluation for any individual patient. Assess the need to evaluate plasmacytomas to confirm response or progression every cycle.
12. Skeletal survey: Results may be used if obtained within 30 days of enrollment. Survey includes: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri.
13. Complete Patient Medication Diary for the study drugs (See Appendix II)
14. AE assessment/toxicity evaluation includes a brief PE when clinically indicated. Patients experiencing drug related adverse events of grade ≥2 should be followed up monthly until the adverse event has resolved to less than or equal to Grade 1 or the event is believed to be chronic or the patient receives other anti-cancer therapy. If the subject will not be visiting the clinic, investigator may consider telephone contact with subject to establish stability and possible toxicities.
15. 30 day Safety follow-up: An adverse events/toxicity evaluation should be completed approximately 30 days (±7 days) following the last cycle of treatment regardless for the reason of discontinuation, unless patient withdraws consent and refuses further evaluation.

4.2 Event Monitoring/Survival Follow-up

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

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

5.0 Grouping Factor:

5.1 Phase: I vs. II

6.0 Registration Procedures

6.1 Registration

6.11 **Phase I – Mayo and non-Mayo institutions – enrollment closed as of Addendum 4**

Prior to discussing protocol entry with the patient, call the MCCC Registration Office [redacted] to insure that a place on the protocol is open to the patient.

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

6.12 **Phase II – Mayo and Non-Mayo institutions - enrollment open as of Addendum 4**

Non-Mayo Institutions:

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

Mayo Institutions only:

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).

All Institutions:

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

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

6.2 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19b and 14.0).

6.3 Verification

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

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.4 IRB approval

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

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

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

6.5 Treatment requirements

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

6.6 Treatment start

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

6.7 Pretreatment

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

6.8 Baseline symptoms

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

6.9a Study drug

Study drug is available on site.

6.9b Blood kits

Blood kit is available on site for this patient.

7.0 Protocol Treatment

This is a sequential phase 1 followed by phase 2 design, which will allow us to assess the MTD of idasanutlin and ixazomib when used in combination, and estimate the efficacy of the combination.

- Study drug dosing will span 3 weeks, with a 1-week "rest" in each 28-day cycle.
- There will be no intra-subject dose escalation. Dose modifications for toxicity are outlined in Section 8.
- All subjects are planned to receive treatment to disease progression, unacceptable toxicity or withdrawal of consent.
- An individual subject will be considered off-treatment following a 30-day safety follow-up period after the last cycle of treatment.

7.1 Treatment Schedule as of Addendum 4

Table 7.1

Drug	Route	Dose	Schedule Each cycle is 28 days
Ixazomib	Oral	Phase 1: As assigned at registration Phase 2: 4.0 mg (MTD from Phase I)	Days 1, 8 and 15
Idasanutlin	Oral	Phase 1: As assigned at registration Phase 2: 200 mg (MTD from Phase I)	Days 1-5
Dexamethasone	Oral	40 mg	Days 1, 8, 15 and 22

7.2 Ixazomib

- Subjects will receive ixazomib weekly for 3 weeks (Days 1, 8 and 15) with a week off of each 28 day cycle.
- Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. The study drug should be taken on an empty stomach, at least 1 hour before or no sooner than 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.
- Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose
- No intra-subject dose escalation of ixazomib will be permitted at any time during study.
- Procedures for ixazomib dose reductions and delays are summarized in Section 8.2, along with the criteria that must be met for retreatment with study drug. If a dose is missed due to toxicity, the dose will not be made up.

- Oral ixazomib is supplied by Takeda Pharmaceuticals. See Section 15.1 for details on ixazomib description, formulation, storage, and accountability.

7.3 Idasanutlin

- Subjects will receive idasanutlin orally once daily on days 1-5 of the 28 days cycle.
- Idasanutlin is taken with water (240mL) on a full or empty stomach. Subjects should not crush or chew tablets. Missed doses will not be made up.
- No intra-subject dose escalation of idasanutlin will be permitted. Procedures for dose reductions and delays are summarized in Section 8.3.
- Idasanutlin is provided by Roche. See Section 15.2 for details on idasanutlin description, formulation, storage, and accountability.

7.4 Dexamethasone

- Dexamethasone may be self-administered by the subject on an outpatient basis.
- Dexamethasone may be permanently discontinued after 12 cycles at the treating physician's discretion or sooner if needed to manage toxicity related to dexamethasone.
- Missed doses of dexamethasone will not be made up. Procedures for dose reductions and delays are summarized in Section 8.4.
- Dexamethasone is commercially available. Accurate records will be kept in the source documents of all drug administration (including dispensing and dosing).

7.5 Treatment at enrolling institution:

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

7.6 Phase I – Determination of Maximum Tolerated Dose (MTD) – **not applicable as of Addendum 4 – Phase I is completed.**

Dose Escalation for individual drugs			
Dose level	**Idasanutlin** PO QD (Days 1-5)	**Ixazomib** PO (Days 1, 8, 15)	**Dexamethasone** PO (Days 1, 8, 15 and 22)
-2	50 mg	3.0 mg	40 mg
-1	100 mg	3.0 mg	40 mg
0*	100 mg	4.0 mg	40 mg
+ 1	200 mg	4.0 mg	40 mg
+2	250 mg	4.0 mg	40 mg
+3	250 mg	5.3 mg	40 mg

*starting dose level

7.61 DLT incidence will be based on toxicity events encountered during the first cycle of treatment with the combination of idasanutlin, ixazomib and dexamethasone.

7.62 Dose escalation or cohort expansion will only take place after 3 patients are fully assessed using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.03 following the completion of Cycle 1.

7.63 Three patients will be treated at each dose level and observed for a minimum of 28 days, to assess toxicities, before new patients are treated. The study will temporarily close. Doses will not be escalated in any individual patient.

7.64 Investigators are to contact the Study Chair as soon as any dose-limiting toxicity (DLT) occurs.

7.65 Definitions of DLT

For this protocol, dose-limiting toxicity (DLT) will be defined as an adverse event attributed as unlikely, definitely, probably, or possibly related in the first cycle to the study treatment and meeting the following criteria:

Toxicity*	***DLT Definition***
Investigations	Grade 4 neutropenia (ANC <500/mm$^{3)}$ for ≥7 days or Grade 4 thrombocytopenia (<25,000/mm$^{3)}$ for ≥7 days
Infection and infestations	Grade 4
Blood and lymphatic system disorders	Febrile neutropenia defined as fever ≥38.5^{o}C (38 >1 hour) with grade ≥3 neutropenia
Other Non-hematologic	≥Grade 3 as per NCI Common Terminology Criteria for Adverse Events v 4.0**
Dose Delay	Any adverse event that causes a dose delay of >2 weeks of the next intended dose
Dose Reduction	Any dose reduction for ixazomib and/or idasanutlin within Cycle 1

*Adverse event attributed as unlikely, definitely, probably, or possibly related to the study medication.

**Grade 3 nausea, vomiting, or diarrhea with maximal supportive treatment(s) will be considered dose limiting.

8.0 Dosage Modification Based on Adverse Events

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

NOTE: If either of idasanutlin or ixazomib is discontinued, the patient can continue on the other drugs, unless specified otherwise in the dose modification tables. If both are discontinued, the patient will go to event monitoring (Section 4.2).

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

8.1 Dose Levels for each drug in the combination

(Based on Adverse Events in Tables 8.2-4)

NOTE: For toxicities that are unrelated to dexamethasone (related to idasanutlin or ixazomib), idasanutlin should be dose reduced at the first instance of the adverse event followed by ixazomib. Thereafter the drugs reduced should alternate between idasanutlin and ixazomib.

NOTE: Once Ixazomib is dose reduced to 2.3 mg, all subsequent dose reductions should be limited to idasanutlin. Patients cannot continue on idasanutlin alone, but can continue on ixazomib alone if idasanutlin is discontinued for toxicity.

NOTE: Toxicities attributable to dexamethasone should lead to dose reduction only for dexamethasone.

Table 8.1 - Dose Reduction Steps for Ixazomib

STARTING Dose	Dose reduction steps for ixazomib		
	Step -1	Step -2	Step -3
4 mg	3 mg	2.3 mg	Discontinue

Table 8.2 - Dose Reduction Steps for Idasanutlin

STARTING Dose	Dose reduction steps for idasanutlin		
	Step -1	Step -2	Step -3
200 mg	100 mg	50 mg	Discontinue

Table 8.3 - Dose Reduction Steps for Dexamethasone

	Dose reduction steps for dexamethasone			
Starting Dose	Step -1	Step -2	Step -3	Step -4
40 mg	30 mg	20 mg	12 mg	8 mg
Dexamethasone may be permanently discontinued after Cycle 12 or at the investigator's discretion due to dexamethasone toxicity.				

If patients cannot tolerate lowest dose level of ixazomib AND idasanutlin they will go to event monitoring per Section 4.2. If dexamethasone is discontinued, the patient may continue treatment.

NOTE: Any study drugs which are discontinued may not be restarted

8.11 Instruction for initiation of a new cycle of therapy or restarting therapy after interruption during a cycle for toxicities

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

- The ANC is ≥1500/μL
- The platelet count is ≥75,000/μL
- Any other non-hematologic treatment -related adverse event that may have occurred has resolved to ≤Grade 1 or baseline severity.

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

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

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

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

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

NOTE: Refer to Section 8.1 for dose levels

Table 8.2

CTCAE System/Organ/ Class (SOC)*	**ADVERSE EVENT**	**ACTION****
Investigations	If platelet count $<30 \times 10^9$/L or ANC $<1.0 \times 10^9$/L or ANC $>1.0 \times 10^9$/L (up to LLN) with fever (temperature >38.5°C)	Days 2-15: Ixazomib dose should be omitted on Day 8 and/or 15 as applicable Complete blood count (CBC) with differential should be followed weekly. If ANC is $\geq 1.0 \times 10^9$/L and/or platelet counts $\geq 30 \times 10^9$/L, ixazomib may be reinitiated with 1 dose level reduction. The subsequent cycle will use the reduced dose.
Skin and subcutaneous tissue disorders	Rash, maculopapular, ≥Grade 2	Omit ixazomib till rash resolves to ≤Grade 1 (See Section 9.9a). Restart at same dose. If the rash recurs, reduce dose by one dose level.
	Any skin, Grade 4	Discontinue ixazomib and remove patient from all study treatment
Nervous System Disorders	Newly developed Grade 1 peripheral neuropathy with pain, ≥Grade 2 peripheral neuropathy	Reduce dose of ixazomib to the next lower dose level

Table 8.2		
CTCAE System/Organ/ Class (SOC)*	**ADVERSE EVENT**	**ACTION****
Nervous System Disorders	Grade 2 neuropathy with pain or Grade 3 peripheral neuropathy	Omit ixazomib until toxicity resolves or returns to baseline. When toxicity resolves, re-initiate ixazomib at the next lower dose level.
	Grade 4 peripheral neuropathy	Omit ixazomib. Peripheral neuropathy should be monitored until toxicity resolves or returns to baseline. Upon recovery, if the patient has received clinical benefit from therapy with ixazomib, the investigator may consider restarting ixazomib at the next lower dose level.
Other	Any other non-hematological Grade 3 attributable toxicity except: Grade 3 nausea and/or emesis in the absence of optimal anti-emetic prophylaxis Grade 3 diarrhea that occurs in the absence of optimal supportive therapy Grade 3 fatigue	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
	Grade 4 Nonhematologic Toxicities	Consider permanently discontinuing ixazomib – Exception if the investigator determines the patient is obtaining a clinical benefit

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

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

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

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

NOTE: Refer to Section 8.1 for dose levels

Table 8.3

CTCAE System/Organ/Class (SOC)*	ADVERSE EVENT	ACTION**
Blood and lymphatic system disorders	Febrile neutropenia associated with fever (≥38.5º C)	• Omit idasanutlin dose. • Follow CBC weekly. • Restart next cycle at one dose level lower for idasanutlin. • If febrile neutropenia is the only toxicity for which a dose reduction is required G-CSF may be used and the idasanutlin dose maintained
Investigations	Grade 3 neutrophil count decreased and sustained for 7 days or Grade 4 neutrophil count decreased Platelet count decreased ≥Grade 3 (platelet count <50,000/mm³)	• Omit idasanutlin dose. • Follow CBC weekly. • Restart next cycle at one dose level lower for idasanutlin. • If neutropenia is the only toxicity for which a dose reduction is required G-CSF may be used and the idasanutlin dose maintained
Skin and subcutaneous tissue disorders	Rash maculopapular Grade 2 or 3	• Omit idasanutlin dose; follow weekly • Restart next cycle at one dose level lower for idasanutlin.
	Any rash Grade 4	• Discontinue idasanutlin and remove patient from all study treatment
Immune system disorders	Allergic reaction Grade 2-3	• Omit dose and follow at least weekly • Restart next cycle at one dose level lower for idasanutlin.
	Grade 4	• Discontinue idasanutlin and remove patient from all study treatment
Other non-hematologic adverse event	Any other non-hematological Grade 3 attributable toxicity except: Grade 3 nausea and/or emesis in the absence of optimal anti-emetic prophylaxis Grade 3 diarrhea that occurs in the absence of optimal supportive therapy Grade 3 fatigue	• Omit idasanutlin 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
Other non-hematologic adverse event	Grade 4 Nonhematologic Toxicities	• Consider permanently discontinuing idasanutlin – Exception if the investigator determines the patient is obtaining a clinical benefit

* Located at http:/ctep.cancer.gov/protocolDevelopment/electronic_applications.ctc.htm
** Use the following to describe actions in the Action column:

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

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

NOTE: Refer to Table 8.1 for dose levels

Table 8.4

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

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

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

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

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

9.0 Ancillary Treatment/Supportive Care

9.1 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

9.3 Nausea and/or vomiting

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

9.4 Blood products and growth factors

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

9.5 Diarrhea

Prophylactic antidiarrheals should be used in this protocol. All patients will receive loperamide 4 mg daily for the first 5 days. 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 (see Section 1.4.3). Volume depletion should be corrected before initiation of study drug. Until further information is available, intake of nonsteroidal anti-inflammatory drugs immediately prior to the administration of ixazomib should be discouraged and requires consultation with the principal investigator. All

necessary supportive care consistent with optimal patient care shall be available to patients as necessary.

9.7 Herpes Zoster prophylaxis

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

9.8 Prohibited medications

9.81 Prohibitedenzyme inhibitors

The following medications and procedures are prohibited during the study: Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted in this study. (Rationale: If there were to be a drug-drug interaction with an inhibitor, the idasanutlin exposure would be increased leading to a high probability of an adverse event.):

- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole
- Strong inhibitors of CYP2C8: anastrozole, montelukast, quercetin, trimethoprim, gemfibrozil, rosiglitazone, pioglitazone

9.82 Prohibitedenzyme 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: Unlike with inhibitors if there were to be a drug-drug interaction with an inducer, idasanutlin or 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 or CYP2C8 inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital. Extra caution should be exercised when using these medications concomitantly and incidence of any side effects should be carefully monitored.

9.83 Systemic treatment with CYP2C8 substrates (e.g. amiodarone, repaglinide, rosiglitazone, sorafenib, and torsemide).

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

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 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 and idasanutlin administration should be modified as noted as per dose modification recommendations in the protocol when thrombocytopenia occurs (see Section 8.2 and Section 8.3). Therapy can be reinitiated at a reduced level upon recovery of platelet counts. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

9.9c Neutropenia

Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable. Growth factor support is not required but may be considered according to standard clinical practice. Idasanutlin and ixazomib administration should be modified as noted as per dose modification recommendations in the protocol when neutropenia occurs (see Section 8.2 and Section 8.3). 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.

10.0 Adverse Event (AE) Reporting and Monitoring

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

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

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

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

WHO:	WHAT form:	WHERE to send:
All sites	**Pregnancy Reporting** http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf	**Mayo Sites** – attach to MCCC Electronic SAE Reporting Form [redacted]

		Will automatically be sent to [redacted] Non Mayo sites – complete and forward to [redacted]
Mayo Clinic Sites	**Mayo Clinic Cancer Center SAE Reporting** [redacted] **AND attach** **MedWatch 3500A (and cover sheet):** http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	Will automatically be sent to [redacted]
Non-Mayo Clinic Sites	**MedWatch 3500A (and cover sheet):** http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf	[redacted]

Definitions

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

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

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

Routine Reporting
Events reported to sponsor via case report forms

Events of Interest

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

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

a. Identify the grade and severity of the event using the CTCAE version 4.0.
b. Determine whether the event is expected or unexpected (see Section 10.2).
c. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
d. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).
e. Determine if other reporting is required (see Section 10.5).
f. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

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

10.2 Expected vs. Unexpected Events

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

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

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
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).

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

10.4 Required Reporting

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

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

Routine Reporting

Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.6.

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

Expedited Reporting

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

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

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

10.41 Special Situations for Expedited Reporting

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events[1]

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

Table 10.411

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

[1] These exceptions only apply if the adverse event does not result in hospitalization or any other serious criteria outlined in Section 10.42. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.
Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

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

10.411 Persistent or Significant Disabilities/Incapacities

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

10.412 Death

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

Reportable categories of Death

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

10.413 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE must be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.414 Second Malignancy

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

10.42 Expedited Reporting Requirements for IND/IDE Agents

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

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

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

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

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

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

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

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

Expedited AE reporting timelines are defined as:

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

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

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

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

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

10.43 General reporting instructions

The Mayo IND and/or MCCC Compliance 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.

Mayo Clinic Cancer Center (MCCC) Institutions:

Use the MedWatch 3500A form (and the MedWatch cover sheet found in the Forms Packet) and Mayo Expedited Event Report form [redacted] for investigational agents or commercial/investigational agents on the same arm.

The MCCC SAE coordinator will submit to Takeda Pharmacovigilance

Fax Number: [redacted]

Email: [redacted]

And submit to Roche at:

Email: [redacted]

Non-MCCC Institutions:

Complete and submit copies of MedWatch 3500A form (and MedWatch cover sheet found in the Forms Packet) to: RSTP2CSAES@mayo.edu and [redacted]

The MCCC SAE coordinator will submit to Takeda Pharmacovigilance

Fax Number: [redacted]

Email: [redacted]

and submit to Roche at:

Email: [redacted]

Note: Sites should not submit reports directly to Takeda or Roche.

10.44 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.

10.441 Special reporting requirements for **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, Shaji Kumar, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB.

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must also be reported in English to 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 http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by 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 http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to 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.

Suggested Reporting Form:

- SAE Report Form (provided by Takeda)
- US FDA MedWatch 3500A: http://www fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default htm
- 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 MedComm Solutions 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

- Phone: [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

10.442 Special reporting requirements for idasanutlin

Roche special requirements for idasanutlin are detailed in the Safety Data Exchange Agreement (SDEA).

- The sponsor-investigator, Shaji Kumar, MD , shall be responsible for: tracking all protocol-defined AE and pregnancy reports,
- evaluating AE and pregnancy reports, providing SAEs, pregnancy reports and AESIs to Roche within 1 business day of the awareness date on a Medwatch/CIOMS form electronically or by fax,
- providing non serious AEs within the final study report upon the completion of the study.
- The parties will ensure that all single case reports have been transmitted to Roche and received by Roche for reconciliation on a monthly basis.
- Investigator shall be responsible for expedited reporting responsibilities for the study as sponsor (regulatory authorities, ethics committee, investigators).
- Investigator, shall be responsible for the preparation of his own DSUR/IND annual report for the study. Roche agrees to forward to Investigator an executive summary of the Roche DSUR upon request for cross referencing.
- Roche shall have the final say and control over safety crisis management issues relating to idasanutlin.
- Roche shall be responsible for activities relating to the IB for idasanutlin.

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 appropriate documentation and use the Mayo Clinic Cancer Center Expedited 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.

Non-MCCC Institutions:

Submit to your IRB as required by your institutional policies.
Submit copies to [redacted]

The MCCC SAE coordinator will submit to Takeda Pharmacovigilance
Fax Number: [redacted]
Email: [redacted]

And submit to Roche at:
Email: [redacted]

The MCCC SAE Coordinator will submit to the sponsor-investigator, [redacted]

The Mayo Clinic Compliance Unit will 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 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 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 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: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportFormUpdated.pdf

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

CTCAE SYSTEM/ORGAN/CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal Disorders	Nausea	X	X

CTCAE SYSTEM/ORGAN/CLASS	Adverse event/Symptoms	Baseline	Each evaluation
	Vomiting	X	X
	# of Stools	X	
	Diarrhea		X
	Constipation		X
Infections and infestations	Sepsis	X	X
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Skin and subcutaneous tissue disorders	Rash, maculopapular	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X

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

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)

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

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

11.0 Treatment Evaluation

11.1 Terms and definitions

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

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

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

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

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

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

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

  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
  - 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-spike) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results** with the exception of defining stringent complete response.

- **Evaluable disease**: Patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike.
- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had "measurable" serum M-spike or urine M-spike, but has had a detectable monoclonal protein in his/her serum and/or urine and/or measurable serum free light chain.
- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

11.2 Clarification of test indications

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

Table 11.2

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

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

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

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

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

11.3 Confirmed response

In order to be classified as an M protein response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be

made by verification on two consecutive determinations.

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

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

11.4 Bone progression:

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

11.5 Response and Progression:

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

Table 11.5

CATEGORY	RESPONSE CRITERIA [a]
Stringent complete response (sCR)[e]	• CR as defined below plus all of the following: • Normal serum FLC ratio • Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence [b] • Not applicable for those patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike at baseline
Complete response (CR)	• Negative immunofixation of the serum and urine • <5% plasma cells in bone marrow • If at on study, the only measurable non-bone marrow parameter was FLC, normalization of FLC ratio
Very good partial response (VGPR)[e]	• PR as defined below plus all of the following: • Serum and urine M-component detectable by immunofixation but not on electrophoresis or • If at on study, serum measurable, ≥90% or greater reduction in serum M-component plus urine M-component <100 mg per 24 h • If at on study, the only measurable non-bone marrow parameter was FLC, ≥90% or greater reduction in the difference between involved and uninvolved free light chain levels • Not applicable for those patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike at baseline

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

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

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

[c] Positive immunofixation alone in a patient previously classified as CR will not be considered progression.

[d] Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

[e] Does not apply to EMD or PCL

[f] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

12.0 Descriptive Factors

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

12.2 Phase I only: Dose level (to be assigned by Registration Office):
-2 vs. -1 vs. 0 vs. 1 vs. 2 vs. 3

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Continuation

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

13.2 Progressive Disease

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

13.3 Off protocol for reasons other than PD

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

13.4 Criteria for Discontinuation of Treatment

Patients may discontinue treatment for the following reasons:

- Progressive multiple myeloma
- Patient refuses further treatment on the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the patient in the patient's best interests
- Patient is lost to follow-up (defined as the inability to contact the patient on 3 separate occasions over 2 years)
- Administrative reasons (e.g., the patient is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation

All attempts should be made to complete the End of Study procedures when the patient discontinues treatment. Patients should go to event monitoring per Section 4.2, unless the patient refuses further study participation or is lost to follow-up.

13.5 Criteria for Study Discontinuation

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

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

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

13.6 Ineligible

A patient is deemed *ineligible* if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered.
If the patient discontinues treatment, the patient will go 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 Off Treatment Form must be submitted. No further data submission is necessary.

13.7 Major violation

A patient is deemed a *major violation*, if protocol requirements regarding treatment in Cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. If the physician decides treatment should be discontinued, the patient will go directly to the event monitoring phase per Section 4.2, and all data up until the point of confirmation of a major violation must be submitted.

13.8 Cancel

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

14.0 Biospecimens

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

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

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)	Study Entry	End of cycle 4	At suspected CR	At PD	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Flow cytometry#	Mandatory	Peripheral blood	EDTA (lavender)	10 mL (1)	See Table 14.2 for time points			X	No	Cool Pak
RNA Seq for p53 driven genes#	Mandatory	Peripheral blood	EDTA (lavender)	10 mL (1)	See Table 14.2 for time points			X	No	Cool Pak
MIC1 ELISA#					See Table 14.2 for time points			X	No	Cool Pak
Genomic studies	Mandatory	Bone marrow aspirate	ACD (yellow)	6 ml (1)	X	X	X	X	No	Cool Pak
Flow cytometry					X	X	X	X	No	Cool Pak

Additional samples on Cycle 1, Day 1 and 6, and Cycle 2, Day 1

14.2 Summary Table of Cycle 1 and 2 Research Blood

	Cycle 1 Day 1				Cycle 1 Day 6	Cycle 2 Day 1			
	Predose (≤1 hour before dosing)	1 hour post-dose (+/-0.25 hr)	3 hrs post (+/-0.5 hr)	6 hrs post (+/-1 hr)	(Post-day 5 dose 24 hours +/-1 hour)	Predose (≤1 hour before dosing)	1hr post (+/-0.25 hr)	3 hr post (+/-0.5 hr)	6 hrs post (+/-1 hr)
Flow cytometry (peripheral blood)	X			X	X				X
RNA Seq and MIC1 ELISA (peripheral blood)	X			X	X				X

14.3 Shipping and Handling

14.31 Kits

14.311 Kits will be used for this study. 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

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

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

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

Predolin Foundation Biobank
Attn: [redacted]
Mayo Clinic
[redacted]
Rochester, MN 55905

14.4 Biomarker Assessments and Rationale:

14.41 Pharmacokinetic studies

We will perform pharmacokinetic studies to examine for any interaction between the drugs in terms of their distribution and elimination.

14.42 Mutational assessment of TP53 remaining allele: TP53 remaining allele mutational assessment in 17pdel patients will be performed as part of Next Generation Sequencing (NGS) of DNA derived from bone marrow aspirate plasma cells pretreatment.

14.43 p53 and/or MDM2 protein levels will be assessed by flow cytometry in the tumor cells derived from bone marrow, blood, as well as peripheral blood lymphocytes. Additionally, other p53 mechanism of action related proteins will be assayed by flow cytometry targeting myeloma cells (CD138+) including but not limited to p21(waf1), BCL2, MYC, PUMA, p16(ink4A).

Post-treatment blood specimens taken at Day5/6 may also be assessed by flow cytometry for same gene products as listed above to establish desired on-target mechanism of action engagement for pharmacodynamic changes.

14.44 MIC1 ELISA: MIC-1 is a secreted protein that is strongly induced by activated p53; its serum levels have been used to assess pharmacodynamic effects consistent with engaged mechanism of action for MDM2 antagonism leading to p53 activation. These will be performed at the time points shown above.

14.45 RNAseq analyses will be performed on baseline derived patient specimens from blood and/or bone marrow. In addition to unsupervised analyses for transcripts associated with response, a supervised analysis will be conducted for MDM2, XPC, BBC3(PUMA,) and p16 (ink4A.) Additionally, RNAseq analyses listed above may also be performed on post-dose specimens on days 5/6 to assess pharmacodynamic changes consistent with mechanism of action target engagement for enhanced p53 activity following administration of drug.

15.0 Drug Information

15.1 Ixazomib

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 capsules are individually packaged in blisters.

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

15.13 **Preparation and storage**: Ixazomib (MLN9708) capsules (0.2 mg, 0.5 mg, 2 mg), individually packaged in blisters, can be stored at 2ºC to 8ºC or "Do not store above 25ºC. Do not freeze." Ixazomib capsules (2.3 mg, 3 mg, 4 mg, and 5.5 mg), individually packaged in blisters, can be stored at "2ºC - 8ºC" or "Do not store above 30ºC. 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.

Capsules of ixazomib will also be referred to as study drug. Study drug will be supplied by Takeda/Millennium as capsules of 2.3-, 3.0- and 4.0 mg ixazomib. Patients should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

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. Ixazomib protein binding was subsequently investigated in plasma samples from 75 cancer patients including those with normal hepatic and renal function (N = 23), with severe renal impairment including patients with end-stage renal disease requiring hemodialysis (N = 18), or with moderate (N = 15) or severe (N = 19) hepatic impairment (Studies C16015 and C16018). These definitive studies demonstrated that ixazomib was 99% bound to plasma proteins and the extent of binding was not altered by severe renal impairment, moderate hepatic impairment, or severe hepatic impairment.

c) Metabolism: Metabolism is expected to be the major mechanism of clearance (CL) of ixazomib as renal clearance contributes approximately 3.7% to CL/F and 6.4% to CL At 0.1 and 0.5 µM substrate concentrations, which are closer to clinical concentrations of ixazomib following oral administration of 4 mg, non-CYP mediated clearance was observed and seemed to play a major role in ixazomib clearance in vitro. At clinically relevant concentrations of ixazomib, no specific CYP isozyme predominantly contributes to ixazomib metabolism and non-CYP proteins may contribute to the clearance of ixazomib in different capacities. Therefore, at clinically relevant concentrations of ixazomib, minimal CYP-mediated DDIs with a selective CYP inhibitor would be expected.

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. A reduced starting dose of ixazomib is recommended for patients with severe renal impairment. 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, popular rash
Uncommon (≥0.1% to <1%): generalized pruritis, generalized rash

Herpes zoster – antiviral prophylaxis should be considered in patients being treated with ixazomib to decrease the risk of herpes zoster reactivation.

Rare but serious risks – intestinal obstruction, life-threatening severe skin rash (Steven Johnson syndrome, TEN, DRESS syndrome), thrombotic thrombocytopenic purpura, tumor lysis syndrome, renal failure, bowel blockage, posterior reversible encephalopathy syndrome, transverse myelitis, progressive multifocal leukoencephalopathy.

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

15.18 **Drug procurement:** Investigational product will be supplied free of charge to trial participants by Takeda/Millennium Pharmaceuticals, Inc.

Ixazomib Destruction: Investigational ixazomib (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

15.2 Idasanutlin

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

15.21 **Background**: Idasanutlin is a selective inhibitor of the tumor suppressor protein 53 (p53) and murine double minute 2 (MDM2) binding that frees p53 from negative control and activates the p53 pathway in cancer cells, which leads to cell cycle arrest and apoptosis in vitro and in vivo.

15.22 **Formulation**: Film-coated tablet at dosage strengths of 50 mg, 200 mg, 300 mg, and 400 mg. The tablets contain RO5503781-020 (spray-dried powder). All tablets contain the excipients copovidone, microcrystalline cellulose, croscarmellose sodium, crospovidone, colloidal silicon dioxide, magnesium stearate, and a film coat. The film coat of the 50 mg as well as 200 mg tablets consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, iron oxide yellow, iron oxide red and iron oxide black. The film coat of the 300 mg dose strength consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, and talc. The film-coat of the 400 mg dose strength consists of polyvinyl alcohol, titanium dioxide, polyethylene glycol, talc, and iron oxide yellow.

15.23 **Preparation and storage**: Film-coated tablets of idasanutlin should be stored under the recommended storage conditions: Do not store above 25°C.

15.24 **Administration:** Refer to the treatment section for specific administration instructions.

15.25 **Pharmacokinetic information**:
Absorption: There was no major effect of high-fat or low-fat food on PK exposure.

Protein binding: 99.99%

Metabolism: The main human CYP enzymes responsible for RO5503781 metabolism are CYP3A4/5 and CYP2C8. CYP3A4 was found to be responsible for the formation of the oxidative metabolites (M1, M2, and M4) of RO5503781 in human liver microsomes, and accounts for approximately 80% of the total metabolism in human liver microsomes.

Half-life elimination: approximately 1 day

Time to peak: 7.5 hours
Excretion: No parent idasanutlin was detected (<1%) in urine samples. Metabolite M4 (RO6802287) was the only major metabolite in human plasma samples. No apparent difference in PK exposure was found between patients with solid tumors and patients with AML in the dose range of 400 to 1600 mg daily × 5 days. PK data from East Asian patients did not appear to differ from other patient ethnicities (mainly Caucasians). Race, Age (23-83), gender, body weight (42.2 − 132.1 kg), body surface area (1.322 −2.64 m^2), concomitant cytarabine administration, disease status (AML vs solid tumor), and creatinine clearance (39.7 − 200.2 mL/min) does not appear to have an impact on PK exposure.

15.26 **Potential Drug Interactions**:

Idasanutlin has a low potential for drug-drug interaction as a perpetrator with CYP1A2, 2C9, 2C19, 2D6, or 3A4, P-gp, BCRP, and CYP2B6 but a higher potential for DDIs with CYP2C8 substrates. Idasanutlin is metabolized by multiple metabolic enzymes, mainly byglucuronidation (65%−80%) and to a lesser extent by oxidation via CYP2C8 and CYP3A4/5. Strong inhibitors and/or inducers of these enzymes may affect idasanutlin exposure. However, a human study with a strong CYP3A4 inhibitor suggested a minimal effect of idasanutlin exposure. CYP2C8 inhibitors are to be avoided when CYP3A4 inhibitors are allowed. Gemfibrozil, an UGT inhibitor, is also a CYP2C8 inhibitor that is excluded. The M4 metabolite of idasanutlin is an OATP B1/3 transporter inhibitor and thus concomitant use of statins should be avoided.

15.27 **Known potential toxicities**:

Very common (≥10%): diarrhea, nausea, vomiting, decreased appetite, thrombocytopenia, neutropenia, febrile neutropenia, sepsis, anemia, pneumonia, pyrexia, fatigue, asthenia, fungal infections, electrolyte disorders (hypokalemia, hypomagnesemia, hypophosphatemia, hypercalcemia, hypernatremia, hypocalcemia, hyponatremia, and hyperphosphatemia)

Common (1%- <10%): tumor lysis syndrome

Uncommon (0.1%- <1%): leukopenia

Serious potential risks: supraventricular arrhythmias, hepatic toxicity, pulmonary embolism

Special populations:
Idasanutlin should not be administered to pregnant women. It is not known whether idasanutlin is excreted in human milk. It has not been studied in pediatric, therefore idasanutlin should not be administered to this patient population
Treatment with idasanutlin in patients with specific medical conditions such as mild heart failure, pulmonary insufficiency, or inadequately controlled diabetes mellitus has not been formally evaluated. It is recommended to avoid treatment in diabetic patients not optimally controlled with medical management (e.g., presence of ketoacidosis).

15.28 **Drug procurement:**

Idasanutlin will be supplied free of charge to trial participants by F. Hoffmann-La Roche LTD.

The Site Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, product presentation and quantity of bottles contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the bottles, and prepare an inventory or drug accountability record.

Investigational idasanutlin (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Drug destruction records must be readily available for inspection by representatives of the MMRC and by regulatory authorities.

15.29 **Nursing Guidelines:**

15.291 Gastrointestinal side effects including diarrhea, nausea, and vomiting were commonly seen. Treat symptomatically and monitor for effectiveness.

15.292 Cytopenias have also been seen. Monitor CBC w/diff and instruct patients to report any unusual bruising or bleeding to study team. Also instruct patients on sign symptoms of infection.

15.293 Pneumonia has been seen. Instruct patients to report any SOB, cough or chest pain to study team immediately.

15.294 Due to early investigation nature of agent, not all side effects can be known at this time. Instruct patients to report any symptoms or side effects to the study team.

15.295 Pyrexia has been reported. Treat symptomatically and monitor for effectiveness.

15.296 Electrolyte abnormalities are common, which may be an early sign of TLS. Monitor CMP and report any abnormalities to the study physician.

15.297 Patients may experience fatigue, instruct in energy conserving lifestyle and monitor for effectiveness.

15.298 Rarely Tumor lysis syndrome has been seen. Monitor electrolytes, especially in patients with high tumor burden.

15.3 Dexamethasone for Oral Administration (DXM)

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

15.32 **Formulation**: Commercially available for oral administration as:

Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg
Solution, oral: 0.5 mg/mL (500 mL)
Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL)

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

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

15.35 **Pharmacokinetic information**:
Onset of action: Prompt
Duration of metabolic effect: 72 hours
Metabolism: Hepatic
Half-life elimination: Normal renal function: 1.8-3.5 hours; **Biological half-life:** 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine and feces

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

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

Common known potential toxicities, frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression

fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

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

16.0 Statistical Considerations and Methodology

16.1 Overview

This is a Phase I/II study of a novel regimen of idasanutlin and ixazomib in combination with dexamethasone in patients with 17p deleted relapsed multiple myeloma. The Phase I study is designed to determine the maximally tolerated dose (MTD) and toxicity profile of ixazomib and idasanutlin in combination with dexamethasone in patients with relapsed multiple myeloma using the standard cohort 3+3 design. The Phase II portion is designed to assess the confirmed response rate associated with therapy with ixazomib and idasanutlin in combination with dexamethasone, in patients with 17p deleted relapsed multiple myeloma.

16.11 Primary Endpoint

The primary endpoint of the phase I portion of this trial is to assess the maximum tolerated dose (MTD) of ixazomib and idasanutlin in combination with dexamethasone.

The primary endpoint of the phase 2 portion is the rate of confirmed response. A confirmed response is defined as a patient who has achieved an sCR, CR, VGPR, or PR on two consecutive evaluations. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation.

16.12 Sample Size

The phase I portion of this study is expected to require a minimum of 9 and a maximum of 24 evaluable patients, but will likely have 15 patients. The 6 patients treated at the MTD in the phase I portion will also be included in the phase II portion. A maximum of 26 additional evaluable patients will be accrued at the MTD dose level for a maximum of 32 evaluable patients in the phase II portion of this study. We anticipate accruing up to 3 additional patients in the phase II portion to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, a maximum of 24 patients will be accrued in the phase I portion and a maximum of 29 patients will be accrued to the phase II portion for an overall maximum of 53 patients for the entire study.

16.13 Accrual Rate and Study Duration

The anticipated accrual rate is 3-4 evaluable multiple myeloma patients per month. At this rate, it will likely take about 2.5 months to enroll, treat, and evaluate each cohort in the phase I portion of this study. The phase I portion is expected to take between 8 and 20 months. The phase II portion of this study will accrue in the subsequent 8-10 months. The maximum total study duration is expected to be approximately 3 years, or until the last patient accrued has been observed for at least 6 months.

16.2 **Phase 1** Study Design

The primary endpoint of the phase I portion of this trial is to estimate the MTD of idasanutlin and ixazomib in combination with dexamethasone. A standard 3+3 phase I design will be utilized. Three patients will be treated at each dose level and observed for a minimum of four weeks (i.e. one full cycle) before new patients are treated. Doses will not be escalated in any individual patient.

16.21 MTD Definition

MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% ($1-(1-0.25)^6$).

Refer to Section 7.65 for definition of dose-limiting toxicity (DLT).

16.22 MTD Determination:

Dose Escalation: The phase I portion of this study will utilize a standard cohort of three design.The dose levels to which patients will be assigned in sequential cohorts are described in Section 7.6.The first cohort of three patients will be treated at dose level 0. Decisions on when and how to dose escalate are described below.

16.221 Three patients will be treated at a given dose level combination and observed for 1 cycle to assess toxicity.

16.222 If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 or 3 of 3 patients treated at a given dose level, then the next 3 patients will be treated at the next lower dose level, if only 3 patients were enrolled and treated at this lower dose level.

16.223 If DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥2 of 6), the MTD will have been exceeded and further accrual will cease to this cohort. If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.

16.224 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

16.225 Dose de-escalation: If dose-limiting toxicity meets the stopping boundaries set by the above dose escalation algorithm at dose level 0 (for example, more than 1 out of 3 patients or more than 1 out of 6 patients), the next cohort of three patients will be entered at a dose level of -1. If dose level -1 meets the stopping boundaries, the next cohort of three patients will be entered at dose level -2. Further dose re-escalation will

depend on the toxicity profile observed at these dose levels, and re-evaluation of the regimen by the study team may be done.

16.226 If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

16.227 Operating Characteristics for standard cohort of 3 design: The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the cohorts of 3 design described above.

True Rate of DLT (%)	Probability of Dose Escalation
10	0.91
20	0.71
30	0.49
40	0.31
50	0.17

16.23 Analysis Plans:

All the relevant results pertaining to toxicity, MTD, response, timed endpoints and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion. The small sample size and the heterogeneous patient population associated with phase I studies restricts the generalizability of the results. Any notable statistical result should only be viewed as preliminary evidence for further study in Phase II trials rather than a definitive finding in and of itself.

16.231 Adverse Events Profile

The number and severity of all adverse events (overall and by dose-level) will be tabulated and summarized in this patient population. The Grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.

16.232 Toxicity Profile

The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level, patient and tumor site will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

16.233 Confirmed response Profile

A confirmed response is defined to be an sCR, CR, VGPR, or PR noted as the objective status on two consecutive evaluations. Confirmed response will be evaluated using all cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have

begun treatment will be evaluable for response. Responses will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as stable and progressive disease in this patient population.

16.3 **Phase II** Statistical Design

16.31 Decision Rule

In previous single agent studies in patients with relapsed or refractory myeloma, response rates of 19-30% have been seen.(Leleu, Karlin et al. 2015) A response rate higher than 25% for idasanutlin and ixazomib in combination with dexamethasone would be of interest in patients with relapsed 17p deleted multiple myeloma.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 25%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 45%. The following one-stage binomial design uses 32 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 25%.

16.311 Final Decision Rule: If 11 or fewer successes are observed in the first 32 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of successes is at least 12, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies.

16.312 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the final decision rule or used in any decision making process. Analyses involving over accrued patients are discussed in Section 16.44.

16.32 Power and Significance Level:
Assuming that the number of successes is binomially distributed, the significance level is .08, i.e. there is a 8% 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) under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.25	0.30	0.35	0.40	0.45
Then the probability of declaring that the regimen warrants further study is…	0.08	0.23	0.45	0.68	0.85

16.33 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

16.4 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.3) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS Standard Operating Procedures,

availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last patient has been followed for at least 6 months.

16.41 Primary Outcome Analyses:

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

16.412 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportion will be calculated.

16.42 Secondary Outcome Analyses

16.421 The rate of CR will be estimated by the number of patients with an sCR or CR or divided by the total number of evaluable patients. The rate of PR will be estimated by the number of patients with a VGPR or PR divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true success proportions will be calculated.

16.422 Overall survival is defined as the time from registration to death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1958).

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

16.424 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.

16.43 Correlative Analyses: Due to the small overall sample size, the results of these analyses will be considered exploratory and hypothesis-generating in nature.

16.431 Effect of inhibition of mdm2 will be assessed by measuring MIC levels. MIC levels at each time point and changes after treatment will be both graphically and quanitatively summarized and explored. Changes from baseline will be evaluted using Wilcoxon’s signed rank test.

16.432 Impact of mdm2 inhibition on activation of p53 and clonal selection will be examined using gene expression profiling and exome sequencing.

16.433 Potential biomarkers associated with response will be assessed in an exploratory manner.Potential markers will be determined using gene

expression profiling.The correlation between potential biomarkers and response (responders vs. non-responders) will be evaluated using Fisher's exact and Wilcoxon rank sum tests, where appropriate.

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

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.

16.521 Phase I (includes all phase I patients):

By the nature of the "cohorts of three" phase I study design, stopping rules are in place for each dose level. Specifically, if 2 or more dose-limiting toxicities (DLTs) are observed during cycle 1 at any given dose level, accrual to that dose level will be stopped, and patients will be accrued to the next lower dose level until a maximum of 6 patients are treated at the lower level. Note that a DLT that affects dose escalation is only that which is observed in the first cycle of treatment. However, all cycles will be reviewed and the study team will determine whether the dose level needs to be adjusted for future patients if ≥2 in the first 3 patients OR ≥3 in the first 6 patients experience a Grade 4 or higher non-hematologic adverse event with an attribution of unlikely, possibly, probably, or definitely related to treatment over all cycles at any given dose level.

16.522 Phase II (includes all phase II patients, including phase I patients treated at the MTD):

Accrual will be temporarily suspended to this study if at any time we observe events with an attribution of unlikely, possibly, probably, or definitely related to study treatment that satisfy one of the following:

- if 7 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event
- if after the first 15 patients have been treated, 40% of all patients experience a grade 4 or higher non-hematologic adverse event.

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

16.6 Results Reporting on ClinicalTrials.gov:

At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on www.ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 3 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has been followed for at least 6 months.

16.7 Inclusion of Women and Minorities

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

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

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

16.731 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	18	34	0	52
Ethnic Category: Total of all subjects*	18	35	0	**53**
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	17	34	0	51
Racial Category: Total of all subjects*	18	35	0	**53**

Ethnic Categories:

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

Not Hispanic or Latino

Racial Categories:

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

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

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

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

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

17.0 Pathology Considerations/Tissue Biospecimens

None

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

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

18.2 Event monitoring

See Section 4.2 and data submission table in the case report form packet for the event monitoring schedule.

18.3 CRF completion for non-Mayo Clinic sites

This study will use Medidata Rave® for remote data capture (rdc) of all study data.

18.4 Site responsibilities

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

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

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

For patients who progress after study therapy supporting documentation may include any of the following: SPEP, UPEP, FLC, serum and urine immunofixation, bone marrow biopsy and aspirate, and X-ray skeletal survey.

18.6 Labelling of materials

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

18.7 Incomplete materials

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

18.8 Overdue lists

A list of overdue materials is automatically available to each site at any time. A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor/participant will be responsible to 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

19.2 Tests to be research funded: None

19.3 Other budget concerns: None

20.0 References

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Appendix I ECOG Performance Status

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

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

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

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

Appendix II Patient Medication Diary

Name **Study ID**

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

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

Please drink at least 6 to 8 cups of liquid per day to help drug absorption. Swallow pills whole, with water, and do not to break, chew, crush or open the pills. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each pill should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the pills.

If you experience any health/medical complaints or take any medication other than idasanutlin, 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***
Idasanutlin							
Ixazomib							
Dexamethasone							

Week of: _____

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

Week of: _____

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

Week of: _____

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

Patient Signature: _____

My next scheduled visit is: _____

If you have any questions, please call: _____

Study Coordinator Use Only

Verified by _____ Date _____

Appendix III Drug Classification Guide

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

IMiDs (immune modulatory drugs)

Thalidomide	Thalidomid	
Lenalidomide	Revlimid	CC-5013
Interferon		
Pomalidomide	Pomalyst	
Levamisole		

Proteasome inhibitors

Bortezomib	Velcade	
Carfilzomib	Kyprolis	
Ixazomib	Ninlaro	MLN9708
Oprozomib		

Topoisomerases

Etoposide	VP-16

Taxanes

Paclitaxel	Taxol
Docetaxel	Taxotere

Monoclonal Antibodies

Anti-SLAMF7	Elotuzumab
Anti-38	Daratumumab

Vinca Alkyloid

Vinblastine
Vincristine
Vindestine
Vinorelbine

Appendix IV Cockcroft-Gault Equation

For males:

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

For females:

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

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

Appendix V MC1582 Model Consent

MC1582 Model Consent Form

***NOTES FOR LOCAL INVESTIGATORS:**

- *The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The website address for this document is* http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- *A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.*
- *Instructions and examples for informed consent authors are in [italics]. Remember to remove these items before finalizing your consent form.*
- *The language should be written in 6th grade language. When proofreading the consent form, ask yourself if an average 6th grader would understand the study after reading this form.*
- *Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials." This pamphlet may be ordered on the NCI website at* https://cissecure.nci.nih.gov/ncipubs/ *or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.*
- *Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.*

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

RESEARCH PARTICIPANT CONSENT AND PRIVACY AUTHORIZATION FORM

Study Title: Phase 1 / 2 trial of idasanutlin in combination with ixazomib and dexamethasone in patients with 17p-deleted relapsed multiple myeloma

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

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

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

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

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

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

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

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

CONTACT INFORMATION

You can contact …	At …	If you have questions or about …
Principal Investigator: *Insert local PI Name* **Study Team Contact:** *Insert local contact here*	**Phone:** *Insert local telephone* **Phone:** *Insert local telephone* **Address:** *Insert local address*	▪ Study tests and procedures ▪ Research-related injuries or emergencies ▪ Any research-related concerns or complaints ▪ Withdrawing from the research study ▪ Materials you receive ▪ Research-related appointments
Institutional Review Board (IRB)/Research Ethics Board (REB)	**Phone:** *Insert IRB/REB telephone* **Toll-Free:**	▪ Rights of a research participant

You can contact …	At …	If you have questions or about …
Research Subject Advocate (The RSA is independent of the Study Team)	**Phone:** *Insert local telephone* **E-mail:**	▪ Rights of a research participant ▪ Any research-related concerns or complaints ▪ Use of your Protected Health Information ▪ Stopping your authorization to use your Protected Health Information
Research Billing	*Insert local telephone*	▪ Billing or insurance related to this research study

Other Information:

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

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

You are being asked to take part in this study because you have been diagnosed with a type of blood cancer called "multiple myeloma" that requires treatment. In addition, your myeloma cells have a particular abnormality in the chromosomes that makes your multiple myeloma harder to treat.

About 53 people will take part in this research study.

2. Why is this research study being done?

This research study is being done to see if the combination of two new drugs will allow better control of multiple myeloma where the cancer cells have lost a part or all of a chromosome (chromosome 17), a situation that is difficult to treat with the current standard treatment.

In this study, you will be treated with a combination of two drugs called ixazomib and idasanutlin. It is thought that ixazomib will interfere with the process of protein breakdown in the multiple myeloma cells. Idasanutlin can make the myeloma cells more sensitive to treatment with other drugs like ixazomib, by masking the effect of the lost chromosome. The combination of drugs used in this study are considered investigational, which means they have either not been approved by the Food and Drug Administration (FDA) for routine clinical use or for the use described in this study. This study is being done to find out what effects (good and bad) the

combination of ixazomib and idasanutlin with dexamethasone has on you and your multiple myeloma.

3. Information you should know

Who is Funding the Study?

Takeda/Millennium Pharmaceuticals and Roche Pharmaceuticals are funding the study. Takeda/Millennium and Roche will pay the Multiple Myeloma Research Foundation/Multiple Myeloma Research Consortium (MMRF/MMRC) to cover costs related to running the study.

Information Regarding Conflict of Interest:

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

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

You will be in the study for approximately three years. You will be in the study for as long as your multiple myeloma is responding to the treatment and you are not having side effects that cannot be managed.

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

If you agree to be in the study, you will be asked to participate in the following tests and procedures. These tests and procedures are part of regular care for multiple myeloma:

Prior to Registration

- Physical exam including complete medical history, height, weight and vital signs (blood pressure, heart rate, pulse, etc.)
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood and urine tests
- Skeletal survey (X-ray or low dose whole body CT)

- Electrocardiogram (ECG)
- Chest x-ray
- Pregnancy test
- Bone marrow aspirate and biopsy

As part of this study, you will also have the following tests and procedures.

- Research blood tests (less than 2 tablespoons) – these will be drawn at the same time as your clinical care
- Research samples (bone marrow and blood) – these samples will be from the bone marrow aspirate and biopsy done for your clinical care

Every Cycle Pre-treatment

- Routine blood and urine tests
- Physical exam including medical history, weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Medication diary

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

End of Cycle 4

- Bone marrow aspirate and biopsy for clinical care to see how your disease is responding to treatment
- Research samples (bone marrow and blood) – taken at the same time as the clinical bone marrow aspirate and biopsy

End of Treatment

- Physical exam including medical history, weight and vital signs
- ECOG performance status (assessment of your ability to carry out daily activities)
- Routine blood and urine tests
- Medication diary
- Bone marrow aspirate and biopsy
- Research samples (bone marrow and blood) – taken at the same time as the clinical bone marrow aspirate and biopsy

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

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

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

As with any medication, allergic reactions are a possibility.

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

Common risks of ixazomib (events occurring greater than 20% of the time)
- Feeling sick to your stomach (nausea)
- Throwing up (vomiting)
- Loose stools (diarrhea)
- Constipation
- Feeling tired or weak
- Decreased number of blood cells (platelets) that help to clot the blood, which could put you at increased risk of bleeding (thrombocytopenia)
- A low number of white blood cells, which are the infection fighting cells, which could put you at risk for infection (Neutropenia)
- A low number of a particular white blood cell, which is important to the immune system (Lymphopenia)
- Infection including shingles
- Decrease in red blood cells, which are the oxygen carrying cells which could make you feel tired (Anemia)
- Fever
- Infection including shingles
- Skin rash
- Swelling of extremities
- Numbness and tingling (also known as peripheral neuropathy)

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

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

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

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

Rare but serious risks of ixazomib

- Life threatening severe skin rash
- Abnormal heart rhythms
- Worsening of your heart function (congestive heart failure)
- Disorders of your lungs that could be serious enough to result in death
- Liver failure

- Abnormal clotting of the blood in small blood vessels (Thrombotic Thrombocytopenic Purpura (TTP))
- A complication that may occur if the cancer cells die too quickly that includes inappropriate increase or decrease of various natural chemicals in the blood stream, called uric acid, phosphorus, potassium, creatinine, and calcium. Severe tumor lysis can result in kidney failure and may harm muscle or nerve function (tumor lysis syndrome)
- High creatinine and renal failure. The amount of creatinine (a waste product made by your body) in your blood helps your doctor understand how your kidneys are working. High creatinine means your kidneys are having trouble working well. Patients who had lost body water because of vomiting and/or loose stools have had high levels of creatinine indicating that the kidneys were failing to function adequately. In some severe situations, less kidney function may require temporary treatment with a machine that supports the function of the kidney (dialysis).
- Blockage of your bowel function – may require hospitalization to resolve
- Severe rash that can lead to skin peeling and life threatening complications (Stevens Johnson syndrome)
- A condition that can be associated with abnormal neurological function and seizures (posterior reversible encephalopathy syndrome; PRES)
- Inflammation of the spinal cord (transverse myelitis)

Progressive multifocal leukoencephalopathy (PML) has been reported with ixazomib in an oncology patient who had previously received a medication associated with PML. PML is a rare, serious infection of the brain that is caused by a virus. Persons with a weakened immune system may develop PML. PML can result in death or severe disability. It is not known whether ixazomib may have contributed to the development PML in this patient.

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

Potential discomforts and risks of idasanutlin

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

- Diarrhea
- Nausea
- Vomiting
- Decreased appetite
- Fatigue
- Decreased platelet counts
- Fever
- Low white blood cell count with or without fever (neutropenia)
- Low levels of potassium in blood
- Asthenia (weakness)
- Anemia
- Abdominal pain
- Constipation

- Chest pain
- Dry skin
- Pruritus (itchy skin)
- Dry eyes
- Increased blood sugar levels
- Myalgia (muscle pain)
- Flushing
- Increased risk of bleeding

Less likely risks of idasanutlin (events occurring less than 20% of the time)

-
- Cough
- Swelling of extremities
- Headache
- Hypomagnesaemia (low level of magnesium in the blood)
- Hypophosphatemia (low level of phosphorus in the blood)
- Shortness of breath
- Back pain
- Decreased levels of minerals in blood
- Dizziness
- Dry mouth
- Altered taste
- Chills
- Insomnia
- Skin rash
- Mouth sores
- Nose bleeds
- Infections (that can be severe at times)
- Pneumonia
- Dehydration
- Weight loss
- Abnormal liver test
- Low blood pressure
- Difficulty sleeping

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

- Blood clots in lungs
- Abnormal heart rhythm
- Liver damage
- Sepsis (Life threatening infections)
- Tumor lysis syndrome (a condition where rapid destruction of tumor cells lead to abnormal mineral levels in the blood and kidney failure)
- Heart failure

OTHER RISKS

Standard of Care Risks

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

Many side effects go away shortly after the study drugs are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death. Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

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

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

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

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

BIRTH CONTROL, DANGERS OF PREGNANCY AND BREASTFEEDING

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

Acceptable non-hormonal birth control methods include:
- Total sexual abstinence. Abstinence must be for the total duration of the study i.e. from when you sign the informed consent form (ICF) until 90 days after the last dose of study drug

- Male sexual partner who has undergone a vasectomy plus male condom with spermicide. (You will need to confirm that your partner's sperm was tested after the vasectomy procedure and that he was confirmed to be sterile.)
- Tubal occlusion plus male condom with spermicide
- Intrauterine Device (IUD) plus male condom with spermicide

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

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

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

FOR MEN
If not sexually abstinent, men who have female partner(s) of childbearing potential should not father a child. Men must also agree to use an effective method of birth control before starting study treatment, during study treatment, and for 90 days following drug completion. In addition, men should not donate semen or sperm while on study or for 90 days following drug completion.

Many side effects go away shortly after the idasanutlin and ixazomib are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death. Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

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

Taking part in this research study is voluntary. You may decide to stop at any time. You should tell the Principal Investigator if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the Principal Investigator or Mayo Clinic may stop you from taking part in this study at any time:

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

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

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

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

Where to get help:

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

Who will pay for the treatment of research related injuries:

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

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

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

This study may or may not make your health better. While doctors hope that taking idasanutlin and ixazomib with dexamethasone will help, there is no proof of this outcome yet. We do know that the information from this study will help doctors learn more about multiple myeloma. This information could help future cancer patients with a similar condition compared to yours.

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

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

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

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

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

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

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

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

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

If you have questions about any costs to you that may result from taking part in the research, please speak with the Principal Investigator listed in the Contacts section. If you wish, arrangements can be made for you to speak with someone in Patient Financial Services about these costs.

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

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

You will not be paid for your participation in this study.

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

13. What will happen to your samples?

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

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

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

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

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

- Mayo Clinic, the sponsor of this study
- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

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

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

ENROLLMENT AND PERMISSION SIGNATURES

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

	/ /	: AM/PM
Printed Name	Date	Time

Signature

Person Obtaining Consent

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

	/ /	: AM/PM
Printed Name	Date	Time

Signature

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

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