DATE: June 1, 2022

TO: CTEP Protocol and Information Office

FROM: Nisha Joseph, MD

SUBJECT: Amendment #8 in response to Dr. Wright's May 27, 2022 request for a rapid amendment.

SUMMARY OF CHANGES – Protocol

I. Response to Dr. Wright's request for rapid amendment (RRA) for MLN9708 (Ixazomib citrate) dated 5/27/22:

#	Section	Change
1.	Header, Title Page	Updated protocol version date.

2.	10.1.1.1	Replaced the MLN9708 (Ixazomib citrate) CAEPR with version 2.1, March 26, 2022. The following changes were made:
		
		• Added New Risk:
		  • Less Likely: Peripheral sensory neuropathy
		  • Rare but Serious: Thrombotic thrombocytopenic purpura
		  • Also Reported on MLN9708 Trials But With Insufficient Evidence for Attribution: Bile duct stenosis; Bone pain; Bronchial obstruction; Disease progression; Flu like symptoms; Fungemia; Injury, poisoning and procedural complications - Other (femoral neck fracture); Insomnia; Myocardial infarction; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (non-Hodgkin's lymphoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (plasma cell myeloma); Pharyngitis; Retinal detachment; Sepsis; Shingles; Sinusitis; Spinal fracture; Tumor pain
		
		• Increase in Risk Attribution:
		  • Changed to Less Likely from Also Reported on MLN9708 Trials But With Insufficient Evidence for Attribution: Arthralgia; Back pain; Dyspnea; Upper respiratory infection
		
		• Decrease in Risk Attribution:
		  • Changed to Less Likely from Likely: Anorexia; Platelet count decreased; Rash maculo-papular
		  • Changed to Rare but Serious from Less Likely: Edema limbs
		  • Changed to Also Reported on MLN9708 Trials But With Insufficient Evidence for Attribution from Less Likely: Dehydration; Lymphocyte count decreased; Pruritus; White blood cell decreased

	(continued)	• Deleted Risk:
		  • Less Likely: Chills; Mucositis oral
		  • Also Reported on MLN9708 Trials But With Insufficient Evidence for Attribution: Alopecia; Blood lactate dehydrogenase increased; Blood and lymphatic system disorders - Other (pancytopenia); Dry skin; Edema face; Esophageal ulcer; Epistaxis; Erythroderma; Hyperhidrosis; Hyperuricemia; Hypophosphatemia; Ileus; Infections and infestations - Other (oral herpes); Investigations - Other (C-reactive protein increased); Paresthesia; Periorbital edema; Photosensitivity; Pneumonitis; Purpura; Pulmonary hypertension; Rash acneiform; Skin and subcutaneous tissue disorders - Other (acute febrile neutrophilic dermatosis); Skin and subcutaneous tissue disorders -Other (erythema nodosum); Skin and subcutaneous tissue disorders - Other (skin discoloration); Skin and subcutaneous tissue disorders - Other (skin fibrosis); Skin hyperpigmentation; Skin induration; Skin ulceration; Urticaria; Vasculitis; Weight loss

SUMMARY OF CHANGES – Consent Forms

II. Dose Escalation Consent form:

#	Section	Change
1.	Header	Updated version date.

2.	What risks can I expect from taking part in this study?	In response to Dr. Wright's request for rapid amendment, the following changes to the risks of MLN9708 were made:
		
		• Added New Risk:
		  • Occasional: Cold symptoms such as stuffy nose, sneezing, sore throat; shortness of breath
		  • Rare: Blood clot which may cause confusion, paralysis, seizures and blindness
		
		• Decrease in Risk Attribution:
		  • Changed to Occasional from Common: Bruising, bleeding; Loss of appetite; Rash
		  • Changed to Rare from Occasional: Swelling of arms, legs
		  • Changed to Also Reported on MLN9708 Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Dehydration; Infection, especially when white blood cell count is low; Itching
		
		• Deleted Risk:
		  • Occasional: Chills; Sores in the mouth which may cause difficulty swallowing

	(continued)	• Provided Further Clarification: • Pain in belly (under Occasional) is now reported as Pain (under Occasional).

III. Dose Expansion Consent form:

#	Section	Change
1.	Header	Updated version date.

2.	What risks can I expect from taking part in this study?	In response to Dr. Wright's request for rapid amendment, the following changes to the risks of MLN9708 were made:
		
		• Added New Risk:
		  • Occasional: Cold symptoms such as stuffy nose, sneezing, sore throat; shortness of breath
		  • Rare: Blood clot which may cause confusion, paralysis, seizures and blindness
		
		• Decrease in Risk Attribution:
		  • Changed to Occasional from Common: Bruising, bleeding; Loss of appetite; Rash
		  • Changed to Rare from Occasional: Swelling of arms, legs
		  • Changed to Also Reported on MLN9708 Trials But With Insufficient Evidence for Attribution from Occasional (i.e., removed from the Risk Profile): Dehydration; Infection, especially when white blood cell count is low; Itching
		
		• Deleted Risk:
		  • Occasional: Chills; Sores in the mouth which may cause difficulty swallowing
		
		• Provided Further Clarification:
		  • Pain in belly (under Occasional) is now reported as Pain (under Occasional).

NCI Protocol #: 10249

Local Protocol #: TBD

ClinicalTrials.gov Identifier: NCT03770260

TITLE: MLN9708 (Ixazomib) and MLN4924 (Pevonedistat) in Relapsed/Refractory Multiple Myeloma Patients: A Phase 1b Trial

Corresponding Organization: **LAO-MD017** / JHU Sidney Kimmel Comprehensive Cancer Center LAO

Principal Investigator:
Nisha Joseph
Emory University
1365B Clifton Road, Suite B400
Atlanta, GA 30322
Telephone: (404)-778-1923
Email: nisha.sara.joseph@emory.edu

Participating Organizations

LAO-11030 / University Health Network Princess Margaret Cancer Center LAO
LAO-CA043 / City of Hope Comprehensive Cancer Center LAO
LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
LAO-MN026 / Mayo Clinic Cancer Center LAO
LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
LAO-OH007 / Ohio State University Comprehensive Cancer Center LAO
LAO-PA015 / University of Pittsburgh Cancer Institute LAO
LAO-TX035 / University of Texas MD Anderson Cancer Center LAO
LAO-NCI / National Cancer Institute LAO

Statistician:
Zhengjia Chen, PhD
Room 342, Grace Crum Rollins Building
1518 Clifton Road, NE
Atlanta, GA 30322
Telephone: (404)-712-8278
Fax: (404)-778-5016
Email: zchen38@emory.edu

Study Coordinator:
Kathryn Clarke
Suite 3012
1365-C Clifton Rd, NE
Atlanta, GA 30322
Telephone: (404)-778-2227
Fax: (404)-778-4389
Email: kathryn.clarke@emory.edu

Responsible Research Nurse:
TBD

LAO Protocol Liaison:
Judy Murray
Johns Hopkins University
201 N. Broadway, Suite 9130
Baltimore, MD 21287
Telephone: (410)-955-4044
Email: jmurra33@jhmi.edu

NCI-Supplied Agent(s): MLN4924 (Pevonedistat) (NSC 793435), MLN9708 (Ixazomib) (NSC 767907)

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:
Original / July 27, 2018
Revision 1 / October 8, 2018
Revision 2 / November 15, 2018
Revision 3 / February 4, 2019
Amendment 1 / April 19, 2019
Amendment 2 / June 24, 2019
Amendment 3 / September 16, 2019
Amendment 4 / November 11, 2019
Amendment 5 / July 13, 2020
Amendment 6 / September 6, 2020
Amendment 7 / August 23, 2021
Amendment 8 / June 1, 2022

SCHEMA

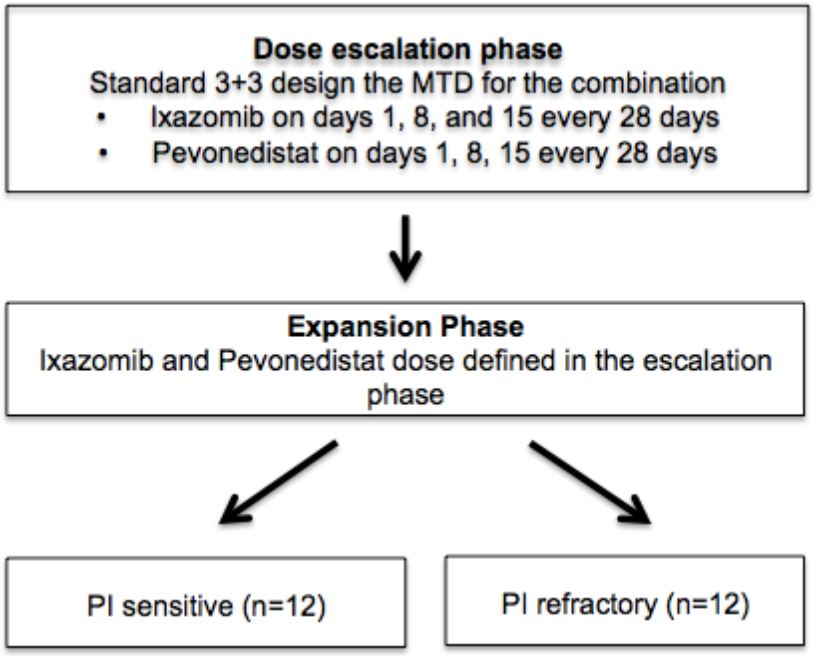

Figure 1: Treatment schema. MTD = maximum tolerated dose, PI = proteasome inhibitor

Dose Escalation Schedule		
Dose Level	**Dose**	
	MLN9708 (Ixazomib) PO QD on Days 1, 8, and 15	**MLN4924 (Pevonedistat) IV on Days 1, 8, and 15***
Level -2	3 mg	15 mg/m^2
Level -1	3 or 4 mg$^{\#}$	15 or 20 mg/m$^{2\#}$
Level 1	4 mg	20 mg/m^2
Level 2	4 mg	40 mg/m^2
Level 3	4 mg	60 mg/m^2
Level 4	4 mg	80 mg/m^2
Level 5	4 mg	100 mg/m^2
PO = by mouth, QD = once daily, IV = intravenous $^{\#}$ Agent attribution for DLT will dictate which drug is dose reduced for dose level -1. No dose reduction below 3 mg for MLN9708 (ixazomib) and 15 mg/m^2 for MLN4924 (pevonedistat) will be allowed. Should a DLT occur attributable to either agent at the lowest dose level, the trial will be stopped. * Dose rounding is allowed as per institutional guidelines.		

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Dose-escalation phase

1.1.1.1 Determine the maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D) of MLN4924 (pevonedistat) in combination with MLN9708 (ixazomib) in relapsed and/or refractory multiple myeloma (RRMM) patients after more than one previous line of treatment.

1.1.2 Dose-expansion phase

1.1.2.1 Describe the safety profile and tolerability of the combination of MLN9708 (ixazomib) and MLN4924 (pevonedistat) in the proteasome inhibitor (PI)-sensitive and PI-refractory populations.

1.1.2.2 Determine the anti-tumor activity and overall response rates (ORR) in patients with RRMM with the use of MLN9708 (ixazomib) and MLN4924 (pevonedistat) in combination.

1.2 Secondary Objectives

1.2.1 Dose-escalation phase

1.2.1.1 Attain pharmacokinetic (PK) characterization of MLN4924 (pevonedistat) in combination with MLN9708 (ixazomib) for the purpose of understanding concentration-effect relationships of both agents.

1.3 Exploratory Objectives

1.3.1 To correlate and predict disease response using the following tests:

- NAD(P)H dehydrogenase (quinone) 1 (NQO1) and cystine/glutamate transporter (SLC7A11) (nuclear factor [erythroid-derived 2]-like 2 [NRF2] target genes): evaluated on whole blood as markers of MLN4924 (pevonedistat) activity.

2. BACKGROUND

2.1 Study Disease(s)

Multiple Myeloma (MM) is the third most common hematologic malignancy with over 30,000 new diagnoses annually and an estimated 12,770 deaths to occur in 2018 (Noone *et al.*, 2018). Though median overall survival (OS) has improved markedly in recent years due to improved therapies, the median progression-free survival (PFS) and OS in PI- and immunomodulatory drug (IMiD)-refractory patients with prior exposure to alkylating agents is 5 and 15 months, respectively (Kumar *et al.*, 2017). Therefore, there is a continued need for effective agents in the relapsed setting.

2.2 CTEP IND Agents

2.2.1 MLN9708 (Ixazomib Citrate)

MLN9708 (ixazomib citrate) (also known as NINLARO®, herein referred to as MLN9708 [ixazomib]), which rapidly hydrolyzes to the biologically active boronic acid MLN9708 (ixazomib) under physiological conditions, is a PI that potently, reversibly, and selectively inhibits the β5 site of the 20S catalytic subunit of the 26S proteasome (Ixazomib Investigator's Brochure, 2017). Proteasome inhibition results in the accumulation of polyubiquitinated substrates, such as cyclin-dependent kinase inhibitors, tumor protein p53 (p53), and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) inhibitory protein (I- κB), within cells (Dalton, 2004; Chauhan *et al.*, 2011). This subsequently leads to increased apoptosis and decreased cell growth and survival, particularly in cancer cells.

2.2.1.1 Nonclinical Experience

MLN9708 (ixazomib) potently inhibits chymotrypsin-like (β5) 20S proteasome activity, with a half-maximal inhibitory concentration (IC_{50}) of 3.4 nM (Kupperman *et al.*, 2010). Compared to the β5 site, MLN9708 (ixazomib) potency was reduced roughly 10-fold toward the caspase-like β1 proteolytic site, and ≥1000-fold toward the trypsin-like β2 site. Consistent with its potent inhibition of the proteasome, MLN9708 (ixazomib) induced apoptosis and inhibited the viability of human MM cell lines and patient-derived MM cells in a dose-dependent manner (Chauhan *et al.*, 2011). MLN9708 (ixazomib) was shown to affect cell types found in the bone marrow microenvironment, inhibiting the *in vitro* formation and function of osteoclasts, promoting those of bone-forming osteoblasts, and providing benefit in tumor burden control and bone loss prevention *in vivo* (Garcia-Gomez *et al.,* 2014). MLN9708 (ixazomib) has demonstrated activity in a range of xenograft models of MM, lymphoma, and solid tumors grown in immunocompromised mice, as well as in transgenic mouse models of plasma cell malignancy (PCM) (Ixazomib Investigator's Brochure, 2017).

Company-sponsored PK studies in rats, rabbits, dogs, and monkeys after intravenous (IV) dosing demonstrated that MLN9708 (ixazomib) had a very low blood clearance, a steep initial distribution phase, and a terminal half-life ($t_{1/2}$) >24 hours (Ixazomib Investigator's Brochure, 2017). MLN9708 (ixazomib) had a higher plasma clearance than in blood, largely because of

extensive concentration-dependent red blood cell partitioning. Metabolism via hydrolysis, hydroxylation, dehydrogenation, and *N*-dealkylation appear to be major routes of MLN9708 (ixazomib) elimination.

Oral (PO) dosing studies in rats and dogs showed that the MLN9708 (ixazomib) plasma concentration increased in an approximately dose-proportional or less than dose-proportional manner, with slight accumulation after repeat dosing (Ixazomib Investigator's Brochure, 2017). Dose-limiting toxicity (DLT) was primarily related to gastrointestinal (GI) and lymphoid systems. Alterations in leukocyte and coagulation parameters consistent with an inflammatory response were also seen at doses below those associated with DLT. Neuronal degeneration of the sympathetic, dorsal root, and end organ ganglia was seen mainly in dogs (probably as a result of higher exposure). In general, the effects seen in the PO toxicology studies in both rats and dogs at tolerated doses were reversible or reversing. The effects seen in IV studies were largely consistent with those of the PO-dosing studies.

2.2.1.2 Clinical Experience

MLN9708 (ixazomib) is the first investigational PO PI to receive regulatory approval (Ixazomib Investigator's Brochure, 2017). The MLN9708 (ixazomib) clinical development program has included both IV and PO formulations. Please refer to the MLN9708 (ixazomib) Investigator's Brochure for details on the IV formulation. Only the PO formulation is commercially available and will be used for clinical trials going forward. As of March 27, 2017, exposure and safety data are available from 779 patients with hematologic and nonhematologic malignancies who have received at least one dose of PO MLN9708 (ixazomib) in phase 1, 1/2, or 2 trials. In addition, serious adverse event (SAE) and death data are available from 2,682 patients enrolled in ongoing phase 3 clinical trials with PO MLN9708 (ixazomib).

2.2.1.2.1 Clinical Pharmacology

After either once- or twice-weekly (QW and BIW, respectively) PO dosing, MLN9708 (ixazomib) is rapidly absorbed with a median first time of maximum observed plasma concentration (T_{max}) of approximately 1 hour post dose (Ixazomib Investigator's Brochure, 2017). The plasma exposure (area under the concentration-time curve [AUC]) of MLN9708 (ixazomib) increases in a dose proportional manner over a dose range of 0.2-10.6 mg based on a population PK analysis performed using data from patients treated with either IV or PO MLN9708 (ixazomib). The population PK analysis also estimated the absolute PO bioavailability for MLN9708 (ixazomib) to be 58%, the steady state volume of distribution to be 543 L, and the geometric mean terminal $t_{1/2}$ as 9.5 days. Based on measured PK parameters and the population PK model, it can be inferred that MLN9708 (ixazomib) is a low clearance drug, with an apparent plasma oral clearance (CL/F) of 3.21 L/hour. Population PK analyses demonstrated that MLN9708 (ixazomib) can be administered as a fixed dose rather than using body surface area (BSA)-based dosing because there was no significant effect of BSA on MLN9708 (ixazomib) clearance.

MLN9708 (ixazomib) has been classified, according to the Food and Drug Administration (FDA) Biopharmaceutical Classification System (BSC), as a Class 3 compound (*i.e.*, high

solubility, low permeability) (Ixazomib Investigator's Brochure, 2017). A high-fat meal reduced the MLN9708 (ixazomib) maximum observed plasma concentration (C_{max}) by 69% and the AUC from time 0 to 216 hours post dose by 28%. Therefore, MLN9708 (ixazomib) should be taken at least 1 hour before or at least 2 hours after food. Metabolism by multiple cytochrome P450 (CYP) enzymes and non-CYP proteins is expected to be the major clearance mechanism for MLN9708 (ixazomib). Analysis of clinical data indicates that the PK properties of MLN9708 (ixazomib) are not affected by co-administration of either strong CYP3A or CYP1A2 inhibitors. At clinically relevant concentrations of MLN9708 (ixazomib), minimal CYP-mediated drug-drug interactions (DDIs) with a selective CYP inhibitor are expected. Similarly, the potential for MLN9708 (ixazomib) to produce DDIs via CYP isozyme induction or inhibition is low. However, reported data from a clinical DDI study with rifampin showed that MLN9708 (ixazomib) C_{max} and AUC from time 0 to the time of the last quantifiable concentration were reduced in the presence of rifampin by approximately 54% and 74%, respectively (NINLARO® Package Insert, 2015). As a result, the co-administration of strong CYP3A inducers with MLN9708 (ixazomib) should be avoided (Gupta *et al*., 2015). MLN9708 (ixazomib) is unlikely to cause or be susceptible to clinical DDIs with substrates or inhibitors of clinically relevant drug transporters (Ixazomib Investigator's Brochure, 2017). PK parameters for MLN9708 (ixazomib) co-administered with lenalidomide plus dexamethasone (LenDex) appear to be similar to those observed when MLN9708 (ixazomib) is administered as a single agent.

Mild or moderate renal impairment (creatinine clearance [CrCL] ≥30 mL/min) and mild hepatic impairment (total bilirubin <1.5 times the upper limit of normal [ULN]) did not alter the PK of MLN9708 (ixazomib) based on the results of a population PK analysis (Ixazomib Investigator's Brochure, 2017). As a result, no dose adjustment is required for these patients. However, a reduced starting dose of MLN9708 (ixazomib) is recommended in patients with severe renal impairment, end-stage renal disease requiring dialysis, moderate hepatic impairment, or severe hepatic impairment. A pooled analysis of data from four phase 1 clinical trials indicates that the pro-arrhythmic risk associated with MLN9708 (ixazomib) is low, with no impact of clinically-relevant MLN9708 (ixazomib) dose or exposure on the corrected time between the start of the Q-wave and end of the T-wave (QTc) prolongation.

2.2.1.2.2 Clinical Safety

Preliminary clinical data are available as of March 27, 2017 for a total of 3,623 patients across 26 studies, 24 of which administered PO MLN9708 (ixazomib) (Ixazomib Investigator's Brochure, 2017). The emerging safety profile indicates that MLN9708 (ixazomib) administration can lead to adverse events (AEs) that are generally manageable and reversible with dose reduction and supportive care. Overall, the observed AEs are generally consistent with the class-based effects of proteasome inhibition. Based on clinical experience from phase 1 studies, the dose recommended for phase 3 studies is 4 mg PO given QW for 3 weeks in a 28-day cycle. Common DLTs included vomiting, nausea, diarrhea, neutropenia, and thrombocytopenia.

As of March 27, 2017, data for the PO formulation of MLN9708 (ixazomib) (administered as monotherapy or in combination with other agents) are available for 779 patients treated in phase 1, 1/2, and 2 trials (Ixazomib Investigator's Brochure, 2017). The most common (>20% of patients) AEs across PO MLN9708 (ixazomib) trials were nausea (43%), diarrhea (43%), fatigue

(39%), vomiting (33%), thrombocytopenia (27%), constipation (25%), decreased appetite (22%), and anemia (23%).

Study drug-related AEs were reported for 84% of patients in the PO formulation studies, and 49% of patients experienced a study drug-related AE of Grade 3 or higher (Ixazomib Investigator's Brochure, 2017). Most of these AEs were in the SOCs of GI disorders (59% any Grade, 10% Grade ≥3), general disorders (43% any Grade, 8% Grade ≥3), blood and lymphatic system disorders (38% any Grade, 27% Grade ≥3), or nervous system disorders (37% any Grade, 4% Grade ≥3). The most common preferred terms included nausea (35% overall, 3% Grade ≥3), diarrhea (32% overall, 6% Grade ≥3), fatigue (28% overall, 6% Grade ≥3), vomiting (25% overall, 3% Grade ≥3), and thrombocytopenia (24% overall, 16% Grade ≥3).

As of March 27, 2017, out of the overall safety population in monotherapy and combination studies with oral MLN9708 (ixazomib) (N = 3447), 625 patients reported at least one AE that resulted in discontinuation of at least one of the drugs in the study drug regimen (Ixazomib Investigator's Brochure, 2017). The most common of these events were peripheral neuropathies asthenic conditions, thrombocytopenia, pneumonia, diarrhea, acute kidney injury, neutropenia, septic shock, general physical health deterioration, maculopapular rash, insomnia, anemia, and plasma cell myeloma. As of March 27, 2017, at least one SAE has been reported for 1482 of 3607 (41%) patients in the safety populations across all company-sponsored clinical studies. The most common SAEs include pneumonia, pyrexia, diarrhea, acute kidney injury, pulmonary embolism, thrombocytopenia, back pain, atrial fibrillation, anemia, and bronchitis. Of the reported 167 deaths that occurred on PO MLN9708 (ixazomib) studies, 23 were considered at least possibly related to study treatment (though not necessarily related to MLN9708 [ixazomib]).

Clinical data regarding the AEs experienced during single-agent PO MLN9708 (ixazomib) therapy are available from studies in RRMM, relapsed and/or refractory systemic light-chain amyloidosis (RRAL), and non-Hodgkin lymphoma (NHL) (Ixazomib Investigator's Brochure, 2017). Overall, the most common AE frequencies were fairly similar between the four trials, though rash was more common with BIW dosing than with QW dosing.

As of March 27, 2017, the most common SAEs reported across six MLN9708 (ixazomib) single-agent trials varied (Ixazomib Investigator's Brochure, 2017). In RRMM trials, the most common SAEs regardless of causality were pneumonia, pyrexia, diarrhea, thrombocytopenia, and dehydration. In newly diagnosed MM patients receiving MLN9708 (ixazomib) or placebo, the most common SAEs included pneumonia, pyrexia, herpes zoster, plasma cell myeloma, influenza, lower respiratory tract infection, back pain, diarrhea, acute kidney injury, and plasmacytoma. In a single-agent MLN9708 (ixazomib) trial conducted in patients with RRAL, the most common SAEs were pleural effusion, atrial fibrillation, and congestive cardiac failure. The most common SAEs in a single-agent trial in NHL were asthenia, diarrhea, vomiting, and bronchopulmonary aspergillosis.

MLN9708 (ixazomib) has been tested in the following combinations: 1) with LenDex, 2) with cyclophosphamide plus dexamethasone, 3) with dexamethasone alone, and 4) with melphalan plus prednisone (Ixazomib Investigator's Brochure, 2017). All but the melphalan plus

prednisone combination have been investigated in phase 2 or 3 trials. As of March 27, 2017, SAE data is available from completed or ongoing trials of all four combinations. Pneumonia was consistently the most common SAE. The AEs in the combination studies were consistent with the safety profile of the individual agents in the combination regimen (*e.g.*, myelosuppression was common in regimens containing melphalan and rash was common in regimens containing lenalidomide). While some of these potential toxicities may be severe, they can be managed by clinical monitoring and standard medical intervention.

As of March 27, 2017, treatment-emergent AE data are available for two phase 1/2 and one phase 3 company-sponsored trials combining MLN9708 (ixazomib) with LenDex to treat patients with RRMM or newly-diagnosed MM (Ixazomib Investigator's Brochure, 2017). On each trial, the most common AEs included diarrhea, constipation, fatigue, nausea, and edema peripheral. The most common Grade ≥3 AEs varied across trials, and included neutropenia, thrombocytopenia, diarrhea, fatigue, lymphopenia, hyperglycemia, hyponatremia. In the phase 3 study in RRMM patients, the incidence of herpes zoster reactivation was 8% in the MLN9708 (ixazomib) plus LenDex regimen and 3% in the placebo plus LenDex regimen for patients who did not receive antiviral prophylaxis; this was compared to <1% for either regimen with antiviral prophylaxis.

As of March 27, 2017, at least 1 Grade ≥3 AE was reported for (67%) patients on a trial combining MLN9708 (ixazomib) with cyclophosphamide and dexamethasone to treat patients with newly-diagnosed MM who were ineligible for high-dose therapy followed by autologous stem cell transplantation (Ixazomib Investigator's Brochure, 2017). The most common of these events included neutropenia (20%), anemia (13%), and thrombocytopenia (12%). Grade 3 or greater skin toxicities for the rash AEs of special interest included rash macular, rash maculopapular, petechiae, drug eruption, erythema, pruritus allergic, and rash erythematous. Grade 3 or greater peripheral neuropathies were reported in 2 patients (both with events of peripheral sensory neuropathy).

2.2.1.2.3 Clinical Efficacy

The clinical efficacy of MLN9708 (ixazomib)-based induction regimens followed by single-agent MLN9708 (ixazomib) maintenance therapy was evaluated in an integrated analysis of four phase 2 trials conducted in patients with newly-diagnosed MM (Dimopoulos *et al*., 2017). The combined ORR was 93% after induction and 94% after maintenance. The best response rate of complete response (CR) plus very good partial response (VGPR) was 57% (22% CR), which increased to 63% (35% CR/stable CR) after maintenance.

MLN9708 (ixazomib) is currently undergoing phase 3 study in RRMM, newly-diagnosed MM, and RRAL (Ixazomib Investigator's Brochure, 2017). Compared to a placebo-controlled LenDex regimen, MLN9708 (ixazomib) in combination with LenDex significantly improved the PFS of RRMM patients in a pivotal global study (PFS: 20.6 months *versus* 14.7 months; *P*=0.01), as well as in a study of advanced RRMM in China (PFS: 6.7 months *versus* 4.0 months; *P*=0.035) (Moreau *et al.*, 2016; Hou *et al*., 2017). At the time of analysis, there was a significant (*P*=0.001) 139% improvement in OS with MLN9708 (ixazomib) in the Chinese study; OS benefit was not yet demonstrated in the global study.

2.2.2 MLN4924 (Pevonedistat)

2.2.2.1 Background

MLN4924 (also known as TAK 924 and pevonedistat; hereinafter referred to as MLN4924 [pevonedistat]) is a first-in-class, small molecule inhibitor of NEDD8-activating enzyme (NAE) under development for the treatment of malignancies (Pevonedistat Investigator's Brochure, 2017). The NEDD8 conjugation (neddylation) pathway is responsible for much of the regulated protein turnover in the cell, which is similar to the ubiquitin-proteasome pathway (UPP) (Podust *et al.*, 2000; Read *et al.*, 2000). However, UPP is known to regulate a myriad of processes in eukaryotic cells, whereas only a limited number of neddylation substrates have been described to date. VELCADE® (bortezomib) for Injection, a drug that acts by inhibiting the 26S proteasome, has proven utility in the treatment of MM and mantle cell lymphoma (VELCADE Package Insert, 2015). Therefore, it is anticipated that other compounds directed against different components of the UPP and/or the NEDD8 conjugation pathway may prove useful in the treatment of malignancies.

NAE, an E1 ligase, is an essential component of the NEDD8 conjugation pathway, which initiates the neddylation to protein substrates (Pevonedistat Investigator's Brochure, 2017). Specifically, NEDD8 conjugation to cullin dependent ubiquitin E3 ligases (CDLs) is necessary for their activity. The ligases in the NEDD8 conjugation pathway control the timely neddylation of many substrate proteins with important roles in cell cycle progression and signal transduction. The ubiquitination/neddylation of proteins targets them for proteasomal degradation. These cellular processes are relevant to tumor cell growth, proliferation, and survival; as such, inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers by inhibiting the degradation of a subset of proteins that are regulated by the proteasome. In nonclinical studies, treatment of cells with MLN4924 (pevonedistat) results in the accumulation of CDL substrates, followed by a DNA damage response and cell death. MLN4924 (pevonedistat) treatment results in tumor growth inhibition (TGI) in mouse tumor xenograft models of solid tumors, lymphoma, and acute myeloid leukemia (AML).

2.2.2.2 Preclinical Experience with MLN4924 (Pevonedistat)

2.2.2.2.1 Target pharmacology

MLN4924 (pevonedistat) is a potent and selective inhibitor of NAE activity (MLN4924 [pevonedistat] was at least 300- and 1800-fold more selective for NAE than for the closely related ubiquitin activating enzyme and sumo activating enzyme, respectively) (Pevonedistat Investigator's Brochure, 2017). MLN4924 (pevonedistat) treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines derived from acute leukemias, lymphomas, MM, and a range of solid tumor types. Changes in protein levels observed in cultured cells treated with MLN4924 (pevonedistat) were consistent with the inhibition of NAE, in particular, a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CDL substrates, including nuclear factor, erythroid 2 (NFE2)-related factor 2 (NRF2) and chromatin-licensing and DNA-replication factor-1 (Cdt-1). In most cell lines evaluated, NAE

inhibition by MLN4924 (pevonedistat) led to DNA re-replication and accumulation of cells in the S phase of the cell cycle; this resulted in DNA damage and subsequent cell death through apoptosis (Soucy *et al.*, 2009; Lin *et al.*, 2010; Milhollen *et al.*, 2011). When administered in combination with hypomethylating agents azacitidine and decitabine, MLN4924 (pevonedistat) demonstrated synergistic activity in AML cell lines.

MLN4924 (pevonedistat) demonstrated pharmacodynamic and antitumor activity in solid tumor (HCT-116 colon and Calu-6 lung), lymphoma (OCI-Ly10, OCI-Ly19, and PHTX-22L), and AML (HL-60) xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route (Pevonedistat Investigator's Brochure, 2017). Antitumor activity of MLN4924 (pevonedistat) in mice bearing HL-60 and THP-1 tumor xenografts was enhanced by combination treatment with azacitidine. Combination treatment with MLN4924 (pevonedistat) and docetaxel significantly inhibited tumor growth in the PHTX-02B primary human breast cancer model and the LU1143 primary human squamous non-small cell lung cancer (sqNSCLC) xenograft model. Combination treatment with MLN4924 (pevonedistat) and carboplatin in both NCI-H69 human small cell lung cancer (SCLC) xenografts and LU1143 primary sqNSCLC xenografts resulted in significant antitumor activity.

2.2.2.2.2 Safety pharmacology

In vitro assay results indicated a low risk for human ether-à-go-go related gene (hERG) channel inhibition by MLN4924 (pevonedistat) (inhibitory constant [K_i]=17.3 mcM) or its three major circulating metabolites (Pevonedistat Investigator's Brochure, 2017).

A non-Good Laboratory Practices (GLP)-compliant PO toxicity study was performed in Sprague Dawley rats dosed with 150 mg/kg MLN4924 (pevonedistat) on Days 1, 3, and 5 (Pevonedistat Investigator's Brochure, 2017). Minimal to mild pulmonary artery adventitial hyperplasia and correlative increases in pulmonary artery pressure were observed at 24 hours post dose. However, no correlation was observed between severity of the microscopic lesions and increases in pulmonary artery pressure. This finding was not observed in rats dosed IV or SC in studies up to 3 months in duration, so the relevance of this finding to clinical safety is not known.

In a GLP-compliant cardiovascular safety pharmacology assessment in male beagle dogs dosed via IV infusion at 15, 30, or 40 mg/kg (300, 600, or 800 mg/m^2, respectively), MLN4924 (pevonedistat) was not well tolerated at doses ≥30 mg/kg (≥600 mg/m^2) (Pevonedistat Investigator's Brochure, 2017). Mortality and/or moribundity were observed within 24 hours post dose as a result of GI injury at 40 mg/kg. Increased heart rate was observed at all doses. In a separate GLP-compliant, 2-cycle, repeat-dose toxicology study in dogs, no test article-related effects were noted in the electrocardiogram (ECG) data.

2.2.2.2.3 Toxicology

The systemic toxicity of MLN4924 (pevonedistat) was assessed in GLP-compliant repeat-dose studies in rats and dogs (Pevonedistat Investigator's Brochure, 2017). MLN4924 (pevonedistat) was administered via a 30-minute IV infusion or by SC injection for two cycles (5 days of dosing followed by a 14-day nondosing period) or for five cycles (4 doses administered every other day

followed by a 14-day nondosing period). The DLTs in the 2-cycle studies for both species were GI toxicity and bone marrow and lymphoid tissue depletion. In tolerated doses in both species, AEs included GI tract injury with emesis (dogs only) and abnormal excreta, hematologic alterations, and an acute phase response (increased fibrinogen and decreased albumin). Increased new trabecular bone formation was observed in the 2-cycle study, while decreased trabecular bone formation was observed in the 5-cycle study and was considered an adverse finding. Microscopic observations in both species included karyomegaly, apoptosis, and increased mitotic figures occurring in rapidly dividing tissues, including the intestinal tract and bone marrow. Most AEs were resolving or had resolved after a 2-week recovery period.

MLN4924 (pevonedistat) did not result in lethality in either of the 5-cycle studies (Pevonedistat Investigator's Brochure, 2017). The primary adverse test article-related effects in IV dosed dogs included an acute phase response (increased body temperature, decreased albumin, increased globulin, increased monocytes and neutrophils, and increased fibrinogen levels); neutrophilic infiltrates in multiple tissues (liver, intestines, spleen, trachea, Peyer patches, and gallbladder); and in males, vacuolation and degeneration of the seminiferous epithelium of the testes. Most AEs were reversing or had reversed after a 2-week recovery period in both rats and dogs. MLN4924 (pevonedistat) did not induce any local tissue response when administered by IV infusion to rats or dogs. MLN4924 (pevonedistat) was not mutagenic in the bacterial reverse mutation assay (Ames assay).

Microscopic changes were observed in male and female reproductive organs in the GLP compliant repeat-dose toxicology studies in both dogs and rats, therefore MLN4924 (pevonedistat) likely represents a substantial reproductive and developmental hazard (Pevonedistat Investigator's Brochure, 2017).

2.2.2.2.4 Nonclinical pharmacokinetics

MLN4924 (pevonedistat) was extensively partitioned into red blood cells (RBCs) in mice, rats, dogs, monkeys, and humans, most likely as a result of the binding to carbonic anhydrase (CA) in the RBCs (Pevonedistat Investigator's Brochure, 2017). The partitioning was species dependent, concentration dependent, and saturable. MLN4924 (pevonedistat) was highly bound in whole blood and plasma of mice, rats, dogs, monkeys, and humans. No metabolite unique to humans was observed *in vitro*. *In vitro*, MLN4924 (pevonedistat) is predominantly metabolized by the CYP isozyme 3A4. There is potential for DDIs if MLN4924 (pevonedistat) is co-administered with drugs that are CYP3A inhibitors or inducers. MLN4924 (pevonedistat) is neither an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC_{50} >100 mcM and K_i >50 mcM) nor an inducer of CYP1A2, 2B6, or 3A4/5 (at concentrations up to 30 mcM), but is a weak inhibitor of CYP2B6 and 2C8 (IC_{50} = 97.6 and 23.1 mcM, respectively). The major elimination pathway of MLN4924 (pevonedistat) in animals is through the hepatic route. MLN4924 (pevonedistat) is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) in Caco-2 cells. MLN4924 (pevonedistat) is also a weak inhibitor of P-gp (IC_{50} = 41.2 to 56.0 mcM) and BCRP (IC_{50} = 6.3 mcM), but not of MRP2 (IC_{50} >200 mcM). Additionally, MLN4924 (pevonedistat) is not a substrate for organic anion-transporting proteins (OATPs).

Detailed information regarding the nonclinical pharmacology and toxicology is provided in the Pevonedistat Investigator's Brochure.

2.2.2.3 Clinical Experience with MLN4924 (Pevonedistat)

The clinical development program of MLN4924 (pevonedistat) began with four phase 1 studies of single agent MLN4924 (pevonedistat) at doses ranging from 25 to 278 mg/m^2:

- Study C15001 in patients with solid tumors (Sarantopoulos *et al.*, 2016);
- Study C15002 in patients with lymphoma or multiple myeloma (Shah *et al.*, 2016);
- Study C15003 in patients with AML, high-grade myelodysplastic syndrome (MDS), or acute lymphoblastic leukemia (ALL) (Swords *et al.*, 2015);
- Study C15005 in patients with melanoma (Bhatia *et al.*, 2016).

In these studies, toxicity involving multiorgan failure on Cycle 1, Day 1, including SAEs of renal, hepatic, and cardiac failure, some with a fatal outcome, was identified at doses equal to or above 110 mg/m^2 (Pevonedistat Investigator's Brochure, 2017). On the basis of a comprehensive review of the available phase 1 clinical safety data at the time, a revised risk mitigation strategy, including limiting the dose to no higher than 100 mg/m^2 for single agent administration, was implemented across the MLN4924 (pevonedistat) program in October 2012. The current understanding of the renal toxicity observed with MLN4924 (pevonedistat) suggests that it is not a primary event but is likely secondary to hemodynamic changes occurring in the setting of a type of acute phase response. Results from an investigational toxicity study performed to model the Cycle 1, Day 1 findings in rats suggested that an existing pro-inflammatory state in rats driven by administration of a single dose of tumor necrosis factor alpha (TNFα) followed by a single dose of MLN4924 (pevonedistat) was associated with a more robust sepsis-like response. These rats exhibited a robust toxicity that was evidenced by the exacerbation of TNFα- or MLN4924 (pevonedistat) induced microscopic changes in the liver, kidney, heart, and intestine (large and small). Rats dosed with the combination also displayed a profound increase in circulating cytokines and chemokines that correlated with microscopic changes. Overall, this investigational study suggests a potential synergy between inflammatory state and administration of MLN4924 (pevonedistat)-.

As of January 2017, approximately 240 additional patients have been treated with MLN4924 (pevonedistat) in single agent and combination studies, and no Cycle 1, Day 1 SAEs as described above have been observed (Pevonedistat Investigator's Brochure, 2017). The Days 1, 3, and 5 schedule for MLN4924 (pevonedistat) infusion was chosen for further studies. The MTD for that schedule for patients with AML in Study C15003 was determined to be 59 mg/m^2, and the MTD for patients with solid tumors in Study C15001 was determined to be 67 mg/m^2. Current development is focused on MLN4924 (pevonedistat) in combination with standard clinically available therapies in hematologic malignancies and solid tumors. Ongoing studies are as follows:

- Study C15009 (phase 1b) is evaluating the MTD of MLN4924 (pevonedistat) on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine (administered on a 5-on/2-off

[weekend]/2-on schedule) in a 28-day treatment cycle in elderly patients with treatment-naïve AML (Swords R.T., 2014).

- Study C15010 (phase 1b) is evaluating the MTD of MLN4924 (pevonedistat) plus docetaxel, gemcitabine, or the combination of carboplatin and paclitaxel, in patients with solid tumors (Lockhart C.A., 2015; Bauer T.M., 2016).
- Study C15011 (phase 1) is evaluating the effects of CYP3A-mediated inhibition of MLN4924 (pevonedistat) in patients with solid tumors (DDI assessment; Part A). After completion of the DDI assessment portion of the study, patients had the opportunity to continue in the study by participating in Part B (MLN4924 [pevonedistat] plus docetaxel or the combination of carboplatin and paclitaxel).
- Pevonedistat-2001 (phase 2) is evaluating the efficacy and safety of MLN4924 (pevonedistat) plus azacitidine *versus* single-agent azacitidine in patients with higher-risk MDS (HR MDS), chronic myelomonocytic leukemia, and low-blast AML.
- Pevonedistat-1012 (phase 1) is investigating MLN4924 (pevonedistat) as a single agent and in combination with azacitidine in adult East Asian patients with AML or MDS.

The cumulative enrollment in all clinical studies through January 22, 2017, is approximately 451 patients (237 for hematological indications and 214 for solid tumor indications), defined as having received at least 1 dose of study drug (Pevonedistat Investigator's Brochure, 2017).

2.2.2.3.1 Clinical Pharmacokinetics

The clinical PK of MLN4924 (pevonedistat) have been evaluated in four monotherapy phase 1 studies in 96 patients with solid tumors (C15001 and C15005) and 109 patients with hematologic malignancies (C15002 and C15003) (Pevonedistat Investigator's Brochure, 2017). These studies have evaluated the single- and multiple-dose PK of MLN4924 (pevonedistat) administered via IV infusion across the 25 to 278 mg/m^2 dose range and at various daily or intermittent dosing schedules within 21-day treatment cycles.

Plasma concentrations of MLN4924 (pevonedistat) declined in a bi-exponential manner at the end of IV infusion, with little or no drug accumulation following intermittent dosing or once-daily dosing for 5 consecutive days of a 21-day cycle (Pevonedistat Investigator's Brochure, 2017). Mean terminal elimination half-life ($t_{1/2z}$) was estimated to be approximately 10 hours (range 7.7-15.2) across doses and schedules. Consistent with *in vitro* data, MLN4924 (pevonedistat) is extensively partitioned in human blood (mean blood-to-plasma concentration ratio of approximately 65) with whole blood and plasma kinetics declining in parallel over time. MLN4924 (pevonedistat) generally exhibited linear PK over the dose range studied. Observed interindividual variability was generally moderate with 18% to 41% coefficient of variation (CV) for C_{max}, 12% to 56% CV for AUC from time 0 to 24 hours post dose (AUC_{0-24}), and 15% to 33% CV for the AUC from time zero to the end of the dosing interval when MLN4924 (pevonedistat) was administered on Days 1, 3, and 5. Body size influences MLN4924 (pevonedistat) systemic clearance and volume of distribution, thus supporting BSA-normalized dosing to reduce variation in systemic exposure of MLN4924 (pevonedistat) in cancer patients. MLN4924 (pevonedistat) clearance (CL) tended to gradually decrease in elderly patients (by approximately 25% over the 30-90 age range). There was also no apparent effect of renal function status (as assessed by estimated CrCL >30 mL/min) on MLN4924 (pevonedistat) PK.

A population PK analysis was conducted using data from MLN4924 (pevonedistat) single-agent studies and MLN4924 (pevonedistat) in combination with standard-of-care chemotherapy in patients with solid tumor or hematological malignancies (Pevonedistat Investigator's Brochure, 2017). MLN4924 (pevonedistat) plasma concentration-time profiles were well described by a 2-compartment model with linear elimination. BSA was an important predictor of CL, intercompartmental clearance (Q), and both central compartment volume of distribution (V_c) and peripheral compartment volume of distribution (V_p). For a typical patient with a BSA of 1.73 m^2, an alpha half-life of 1.27 hours and a beta (elimination) half-life of 7.85 hours are estimated. Concurrent administration of carboplatin and paclitaxel decreased the CL of MLN4924 (pevonedistat)- by approximately 44%, translating to an approximately 80% higher TAK-924 exposure (AUC) during co-administration with carboplatin and paclitaxel. Co-administration with azacitidine, gemcitabine, or docetaxel did not appear to affect the CL of MLN4924 (pevonedistat). Race, sex, age, tumor type (hematologic *vs.* solid), mild or moderate renal impairment (CrCL ≥30 mL/min), or mildly impaired liver function, to the extent represented in this dataset, had no impact on MLN4924 (pevonedistat) PK.

Additionally, evaluation of MLN4924 (pevonedistat) PK is ongoing for two studies of MLN4924 (pevonedistat) in combination with different standard-of-care therapies, and for a DDI study evaluating the effects of CYP3A-mediated inhibition on MLN4924 (pevonedistat) (Pevonedistat Investigator's Brochure, 2017). MLN4924 (pevonedistat) PK was not altered in the presence of azacitidine when compared to historical single agent data. Also, no obvious changes in the PK behavior of MLN4924 (pevonedistat) in the presence of docetaxel or gemcitabine have been observed, whereas a trend towards increasing plasma concentrations of MLN4924 (pevonedistat) in the presence of carboplatin plus paclitaxel was evident (Lockhart C.A., 2015; Bauer T.M., 2016). This apparent drug interaction effect, which cannot be explained at this time, warrants further understanding of the disposition properties of MLN4924 (pevonedistat) in humans.

In the DDI study, preliminary PK evaluations from 26 patients with advanced solid tumors (MLN4924 [pevonedistat] 8 mg/m^2 [13 patients on fluconazole, 13 patients on itraconazole]) indicated that multiple-dose fluconazole appeared to have a minimal effect on MLN4924 (pevonedistat) PK (13% increased AUC from 0 to infinity [AUC_∞] on average), while systemic exposure of MLN4924 (pevonedistat) appeared to increase by 23% on average in the presence of itraconazole (Pevonedistat Investigator's Brochure, 2017). MLN4924 (pevonedistat) was found to extensively partition in human blood, with a mean blood-to-plasma concentration ratio of about 65, which remained constant throughout the 24-hour sampling period, indicative of rapid equilibrium.

Additional data from 11 patients who completed protocol specified dosing and PK evaluations indicated that MLN4924 (pevonedistat)- systemic exposures following IV administration at 20 mg/m^2 in the presence of itraconazole were similar to those in the absence of itraconazole (Pevonedistat Investigator's Brochure, 2017). On the basis of these results, moderate and strong CYP3A inhibitors and P-gp inhibitors can be used in patients receiving MLN4924 (pevonedistat). For individual studies in the MLN4924 (pevonedistat) clinical program, reference should be made to the respective protocols for specific information relating to excluded and permitted medications.

For detailed information please consult the current Pevonedistat Investigator's Brochure.

2.2.2.3.2 Pharmacodynamics

Preliminary data provide evidence of pathway inhibition downstream of NAE and biological activity of MLN4924 (pevonedistat) in skin and tumor tissue (solid tumor or AML bone marrow derived blasts) at all doses tested in pharmacodynamic assays (Pevonedistat Investigator's Brochure, 2017). These doses range from 25 to 261 mg/m^2 across the various single-agent, phase 1 MLN4924 (pevonedistat) trials.

For detailed information please consult the current Pevonedistat Investigator's Brochure.

2.2.2.3.3 Summary of Safety and Efficacy Data Findings Available on Takeda-Sponsored Trials

For detailed information please consult the current Pevonedistat Investigator's Brochure.

Phase 1 Monotherapy Studies

Overall, 99 patients with advanced solid tumors or melanoma in Study C15001 and Study C15005 were treated with single-agent MLN4924 (pevonedistat) at doses ranging from 25 to 278 mg/m^2 (Pevonedistat Investigator's Brochure, 2017). Common AEs (reported by ≥25% of patients in either study) were fatigue, nausea, anemia, decreased appetite, vomiting, diarrhea, myalgia, constipation, arthralgia, dizziness, and peripheral neuropathy. DLTs included increased enzymes upon liver function tests (LFTs), increased creatinine, acute renal failure and acute hepatic failure, hypophosphatemia, and myocarditis. Acute renal failure occurred in three patients: two patients on Study C15001 at 196 mg/m^2 (one patient also reported acute hepatic failure); and one patient on Study C15005 at 157 mg/m^2, who also reported myocarditis and hyperbilirubinemia. Deaths on study that were considered related to study treatment included multi-organ failure (at 61 mg/m^2 once daily [QD] for 5 consecutive days and 196 mg/m^2 in Study C15001), disease progression (at 83 mg/m^2 in Study C15001), and renal failure acute (at 209 mg/m^2 in Study C15005).

A total of 128 patients with hematologic malignancies (lymphoma, MM, AML, MDS, or ALL) in Study C15002 and Study C15003 were treated with single-agent MLN4924 (pevonedistat) at doses ranging from 25 to 261 mg/m^2 (Pevonedistat Investigator's Brochure, 2017). Common AEs (reported by ≥25% of patients in either study) were alanine aminotransferase (ALT) increased, anemia, aspartate aminotransferase (AST) increased, chills, constipation, decreased appetite, diarrhea, dizziness, dyspnea, fatigue, febrile neutropenia, headache, muscle spasms, myalgia, nausea, peripheral edema, pyrexia, and vomiting. DLTs included increased LFTs, febrile neutropenia, muscle spasms, thrombocytopenia, acute renal failure, orthostatic hypotension, cardiac failure, rash morbilliform, GI necrosis, hypotension, lactic acidosis, and myocardial ischemia. Deaths on study that were considered related to study treatment (all in Study C15003) included two deaths from multiorgan failure (at 110 and 147 mg/m^2), one from sepsis (at 78 mg/m^2), and one from cardiopulmonary failure (at 45 mg/m^2).

The primary aims of the phase 1 monotherapy studies were to establish the safety profile and to determine the MTDs of MLN4924 (pevonedistat) administered by several different dose schedules in both hematologic and solid tumor settings (Pevonedistat Investigator's Brochure, 2017). While safety, PK, and pharmacodynamic objectives were the primary focus of these studies, disease response was also assessed. A total of 12 patients experienced partial responses (PRs) or better in the phase 1 monotherapy studies.

In Study C15003, responses (CRs and PRs) were observed in a variety of patient settings, including postallogeneic transplant, therapy-related AML, and primary refractory AML (Milhollen *et al.*, 2011). Although some of the responses were of relatively short duration, one patient each in the 44 mg/m^2 cohort of Schedule A (dosed on Days 1, 3, and 5), the 83 mg/m^2 MTD cohort of Schedule B (dosed on Days 1, 4, 8, and 11), and the 25 mg/m^2 cohort of Schedule A achieved a remission for 12.3, 10.1, and 5.1 months, respectively (Pevonedistat Investigator's Brochure, 2017). Another patient had stable disease (SD) for 8 cycles, then a PR, followed by a CR for a total of 2.7 months. All 13 patients who received treatment for 5 or more cycles achieved SD or better, ranging from 2.56 to 13.44 months. The duration of SD or better was considered clinically meaningful if the patient had SD or better at Cycle 4, Day 21 and proceeded to Cycle 5.

Phase 1 Combination Studies

Study C15009 is a phase 1b study evaluating the MTD of MLN4924 (pevonedistat) on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28-day treatment cycle in patients 60 years of age or older with treatment-naïve AML who are unlikely to benefit from standard induction therapy (Pevonedistat Investigator's Brochure, 2017). As of January 22, 2017, enrollment had completed and 4 patients remained on study. As of January 22, 2017, preliminary data are available for 64 patients enrolled in the study who received at least one dose of MLN4924 (pevonedistat) in combination with azacitidine; these patients had completed a total of approximately 441 cycles, with a median of four cycles of treatment. In the dose escalation cohorts, six patients received 20 mg/m^2 MLN4924 (pevonedistat), and three patients received 30 mg/m^2. The most common events (reported by ≥25% of patients) were constipation (48%), nausea (42%), fatigue (39%), anemia (39%), febrile neutropenia (31%), decreased appetite (30%), thrombocytopenia (28%), and pyrexia (25%). The MTD in this study was determined to be 20 mg/m^2 MLN4924 (pevonedistat) given on Days 1, 3, and 5, in combination with 75 mg/m^2 azacitidine given on Days 1 through 5, 8, and 9, in 28-day treatment cycles. A total of 45 (70%) patients experienced at least one SAE. A total of 13 SAEs were reported for more than one patient, including: febrile neutropenia (17 patients); pneumonia (9 patients); AML (6 patients); pyrexia (4 patients); sepsis (3 patients); and acute myocardial infarction, cellulitis, diverticulitis, dyspnea, embolism, hypoxia, mental status changes, multi-organ failure, and transaminase increased (2 patients each). A total of 21 patients treated with MLN4924 (pevonedistat) (either 20 mg/m^2 or 30 mg/m^2) discontinued from study participation because of neutropenia. No other events leading to discontinuation were assessed by study investigators as at least possibly related to study drug treatment. Seventeen on-study deaths were reported (within 30 days of the last dose of study drug); none were assessed as related to study treatment. A total of 31 patients (60%)

experienced PR or better. Nineteen patients (37%) had a best response of CR, 5 patients (10%) had a best response of complete remission with incomplete blood count recovery (CRi), and 7 patients (13%) had a best response of PR. One patient in the 30 mg/m^2 dose level group achieved a CR; all other responses occurred in patients treated with 20 mg/m^2.

Study C15010 is a phase 1b study evaluating the MTD of MLN4924 (pevonedistat) plus docetaxel, gemcitabine, or a combination of carboplatin and paclitaxel, in patients with solid tumors (Pevonedistat Investigator's Brochure, 2017). As of January 22, 2017, enrollment has completed; 2 patients remained on study. The treatment arms are:

- Arm 1: MLN4924 (pevonedistat) dosing on Days 1, 3, and 5 with 75 mg/m^2 docetaxel dosing on Day 1 in a 21-day cycle.
- Arm 2 Lead-in: MLN4924 (pevonedistat) dosing on Days 1, 3, and 5 with AUC6 carboplatin dosing on Day 1 in a 21-day cycle.
- Arm 2: MLN4924 (pevonedistat) dosing on Days 1, 3, and 5 with 175 mg/m^2 paclitaxel dosing on Day 1 and AUC5 carboplatin dosing on Day 1 in a 21-day cycle (based on the DLTs in the Arm 2 Lead-in cohort).
- Arm 3: MLN4924 (pevonedistat) dosing on Days 1, 8, and 15 with 1000 mg/m^2 gemcitabine dosing on Days 1, 8, and 15 in a 28-day cycle.

As of January 22, 2017, preliminary data are available for 64 patients enrolled who received at least one dose of MLN4924 (pevonedistat) in combination with standard of care; these patients had completed a total of approximately 366 cycles, with medians ranging from 2 to 6 cycles of treatment across the four treatment groups (Pevonedistat Investigator's Brochure, 2017). The starting dose levels for dose escalation and determination of MLN4924 (pevonedistat) MTD were 15 mg/m^2 for Arm 1 and Arm 2, and 25 mg/m^2 for Arm 3. Overall, the most common AEs (occurring in ≥25% of patients) were fatigue (58%), nausea (50%), anemia (41%), diarrhea (34%), constipation (34%), AST increased (31%), ALT increased (28%), and alopecia (27%).

Per the data cut off, 15 patients experienced Cycle 1 DLTs in Study C15010. Increased ALT or AST (or both) accounted for DLTs in 11 patients, febrile neutropenia was reported for 3 patients, and 1 patient experienced thrombocytopenia (Pevonedistat Investigator's Brochure, 2017). In Arm 3, one event of febrile neutropenia worsened from Grade 3 to Grade 5.

The MTD for Arm 1 was determined to be 25 mg/m^2 MLN4924 (pevonedistat) (dosing on Days 1, 3, and 5 with 75 mg/m^2 docetaxel dosing on Day 1 in a 21-day cycle) (Pevonedistat Investigator's Brochure, 2017). No MTD was determined for the Arm 2 Lead-in per protocol, but these DLTs informed the dose selection for paclitaxel and carboplatin in Arm 2: paclitaxel dose 175 mg/m^2 and a reduced dose for carboplatin of AUC5. The MTD for Arm 2 was determined to be 20 mg/m^2 MLN4924 (pevonedistat) (dosing on Days 1, 3, and 5 with 175 mg/m^2 paclitaxel and AUC5 carboplatin dosing on Day 1 in a 21-day cycle). The gemcitabine combination arm (Arm 3) was closed to enrollment due to lack of tolerability (MTD was not determined). A total of 26 (41%) patients experienced at least one SAE. Febrile neutropenia was the only event reported for at least one patient in each of the four treatment arms (reported for 2 of 26 patients in Arm 2 and 2 of 10 patients in Arm 3). Dyspnea was reported for 3 of the 22 patients in Arm 1 and for 1 patient in Arm 3. Abdominal pain was reported for one patient

each in Arm 1 and Arm 3 and pneumonia was reported for two patients in Arm 1; all other events were reported for only one patient across the treatment arms. Eighteen patients discontinued the study because of treatment-emergent AEs (TEAEs). Events that resulted in study discontinuation that were assessed at least possibly related to study drug treatment included ALT and AST increased, blood bilirubin increased, and blood creatinine increased (one patient each in Arm 1); platelet count decreased (one patient in Arm 2), peripheral neuropathy (two patients in Arm 2); neutropenia (one patient in Arm 2), thrombocytopenia (one patient in Arm 2), leukopenia, lymphopenia, and pneumonitis (one patient each in Arm 3), and febrile neutropenia (two patients in Arm 3). Six on-study deaths (within 30 days of the last dose of study drug) were reported with one death (Arm 3; due to febrile neutropenia) assessed as related to study treatment (MLN4924 [pevonedistat] and gemcitabine).

Twelve patients (22%) on Study C15010 had achieved PR or better (Pevonedistat Investigator's Brochure, 2017). Two (9%) patients in Arm 2 achieved a CR; three (16%) patients in Arm 1, one (17%) patient in the Arm 2 Lead-in, and six (26%) patients in Arm 2 achieved a PR.

In Part A of Study C15011, patients receive a single dose of MLN4924 (pevonedistat) given as an IV infusion on Day 1 and Day 8, and either concomitant oral fluconazole or itraconazole on Day 4 through Day 10 (Pevonedistat Investigator's Brochure, 2017). Patients are assessed for eligibility to continue in Part B (optional) after completion of Part A during a 2- to 8-week washout period. As of January 22, 2017, enrollment is completed. Thirty-six of the 51 patients enrolled in Study C15011 continued into Part B of the study with 4 ongoing as of January 2017; these 36 patients received a total of approximately 203 cycles of MLN4924 (pevonedistat) in combination with either docetaxel (n=23; median 4 cycles; range 2-10) or the combination of carboplatin and paclitaxel (n=13; median 5 cycles; range 2-27). Overall, the most common AEs (occurring in ≥30% of patients in Part A or Part B) were fatigue (45%, 53%), vomiting (45%, 50%), nausea (41%, 50%), decreased appetite (41%, 39%), dehydration (35%, 44%), constipation (33%, 39%), anemia (35%, 33%), stomatitis (Part B, 33%), diarrhea (31%, 39%), headache (Part B, 36%), and hypokalemia (Part B, 31%).

A total of 30/51 (59%) patients experienced at least one SAE. Most SAEs (inclusive of Part A and Part B) were reported for 1 patient only; events reported for 3 or more patients included dyspnea (6 patients); pneumonia (5 patients); abdominal pain, abdominal pain upper, nausea, vomiting, failure to thrive, aspiration pneumonia, hypotension (4 patients each); small intestinal obstruction, and hyperkalemia (3 patients each) (Pevonedistat Investigator's Brochure, 2017). Further details can be found in the current Pevonedistat Investigator's Brochure. Seventeen patients had discontinued the study because of a TEAE, only 1 assessed as related to study treatment in Part A.

As of January 22, 2017, 18 on study deaths (within 30 days after the last dose of study drug) had been reported in Study C15011 as an outcome of an AE (Pevonedistat Investigator's Brochure, 2017). One death (due to respiratory failure) was assessed by the investigator as related to treatment with docetaxel. None of the other deaths were considered related to study treatment.

As of January 22, 2017, 4 patients achieved a PR in Part B of the study. Two patients (breast, mixed ductal/lobular carcinoma; adenocarcinoma of vulva) received MLN4924 (pevonedistat)

with docetaxel; both patients previously received taxane (Pevonedistat Investigator's Brochure, 2017). Two patients (thyroid cancer; thymic cancer) who received MLN4924 (pevonedistat) with carboplatin/paclitaxel had also received carboplatin plus paclitaxel as part of their prior therapy. Five additional patients achieved durable SD (at least five cycles of on-study treatment), including a patient with thymoma who received 29 cycles of treatment with MLN4924 (pevonedistat) plus carboplatin/paclitaxel, with a best response of SD.

In the phase 1 Study Pevonedistat-1012, patients are enrolled in one of four treatment arms:

- Cohort S1 (MLN4924 [pevonedistat] 25 mg/m^2).
- Cohort S2 (MLN4924 [pevonedistat] 44 mg/m^2).
- Cohort C1 (MLN4924 [pevonedistat] 10 mg/m^2 plus azacitidine 75 mg/m^2).
- Cohort C2 (MLN4924 [pevonedistat] 20 mg/m^2 plus azacitidine 75 mg/m^2).

Patients in Cohorts S1 and S2 received MLN4924 (pevonedistat) on Days 1, 3, and 5 in a 21-day cycle (Pevonedistat Investigator's Brochure, 2017). In the combination treatment cohorts, C1 and C2, patients received MLN4924 (pevonedistat) on Days 1, 3, and 5 with 75 mg/m^2 azacitidine dosing on Days 1 through 5, 8, and 9 in a 28-day cycle.

As of January 22, 2017, 10 patients had received therapy (mean, 7.7 doses; median, 6.0 doses) for a total of 27 treatment cycles (mean, 2.7 cycles; median, 2.0 cycles) (Pevonedistat Investigator's Brochure, 2017).

Preliminary data indicates that five patients discontinued (Pevonedistat Investigator's Brochure, 2017). The most common TEAEs (two patients each) were fatigue, dizziness, and febrile neutropenia. Five (50%) patients reported an SAE during the study, with no event reported in more than one patient. Three deaths occurred and were assessed as not related to the study treatment.

Pevonedistat-2001, a phase 2 study, is evaluating the efficacy and safety of MLN4924 (pevonedistat) plus azacitidine *versus* single-agent azacitidine in patients (aged 18 years and older) with HR MDS, chronic myelomonocytic leukemia (CMML), and low blast AML (Pevonedistat Investigator's Brochure, 2017). With a 28-day treatment cycle, MLN4924 (pevonedistat) is administered on Days 1, 3, and 5 at a starting dose of 20 mg/m^2, with azacitidine at a starting dose of 75 mg/m^2 administered on Days 1 through 5, 8, and 9. As of January 22, 2017, 33 patients were treated with the combination of MLN4924 (pevonedistat) plus azacitidine, and 34 patients received azacitidine alone.

As of January 22, 2017, preliminary data are available for the 65 patients enrolled in the study and 61 patients remain on the study (Pevonedistat Investigator's Brochure, 2017). The most common TEAE was nausea, reported by 16 patients (25%). Eighteen (28%) patients reported an SAE. The only SAEs experienced by more than 1 patient in either treatment group were febrile neutropenia (3 patients in the azacitidine treatment group and 1 patient in the MLN4924 (pevonedistat) plus azacitidine treatment group) and pyrexia (2 patients in the MLN4924 [pevonedistat] plus azacitidine treatment group). Two patients were discontinued from the study/study drug because of TEAEs; these events were not considered related to the study

treatment. No deaths occurred in the MLN4924 (pevonedistat) plus azacitidine treatment group. Seven deaths occurred in the azacitidine treatment group; only febrile neutropenia was considered related to treatment.

2.3 Rationale

MLN9708 (ixazomib) is the first orally available PI and has shown more potent pharmacodynamic effects as compared to bortezomib (Kupperman *et al.*, 2010). MLN9708 (ixazomib) binds and inhibits the chymotrypsin-like site of the 20S proteasome, subsequently interfering with the function of the UPP and leading to accumulation of intracellular proteins and cellular stress. MLN9708 (ixazomib) was approved in 2015 for the treatment of RRMM patients after one prior line of therapy in combination with lenalidomide and dexamethasone following a phase 3 clinical trial that demonstrated an improved PFS over lenalidomide and dexamethasone alone (20.6 months *vs*. 14.7 months, *P*=0.01) (Moreau *et al.*, 2016). In the aforementioned TOURMALINE-MM1 study, MLN9708 (ixazomib) was dosed 4 mg weekly on Days 1, 8, and 15 of a 28-day cycle. In a phase 1 study, Richardson *et al*. evaluated twice weekly dosing of MLN9708 (ixazomib), dosed on Days 1, 4, 8, and 11 of a 21-day cycle, and found this dosing schedule to also be well tolerated with durable and prolonged disease responses, with a maximum tolerated dose of 2 mg/m^2 (Richardson *et al.*, 2014).

The clinical efficacy of PIs in the treatment of myeloma has confirmed the therapeutic strategy of targeting the ubiquitin-proteasome pathway and led to attempts to identify targets at different levels of this pathway. MLN4924 (pevonedistat) is a novel small-molecule inhibitor of NAE that regulates protein ubiquitination upstream of the proteasome. NAE catalyzes the initial step in the neddylation pathway, covalent attachment of NEDD8 to cullin-ring ligases (CRLs), the largest family of the E3 ubiquitin ligases. This step is required for activation of CRLs, which then ubiquitinate target proteins for degradation.

MLN4924 (pevonedistat) has demonstrated both *in vitro* and *in vivo* activity in preclinical models. *In vitro* treatment of myeloma cell lines showed a dose- and time-dependent decrease in cell growth (Figure 2) (McMillin *et al.*, 2012; Gu *et al.*, 2014). This response was preserved even when co-cultured with osteoclasts and bone marrow stromal cells, supporting the efficacy of NEDD8 inhibition despite the bone marrow microenvironment. Additionally, MLN4924 (pevonedistat) demonstrated activity in bortezomib-resistant ANBL-6-V5R myeloma cells, with no increased resistance as compared with the parental cell line (ANBL-6). *In vivo*, administration of MLN4924 (pevonedistat) in immunocompromised mice led to a significant reduction in tumor burden (McMillin *et al.*, 2012).

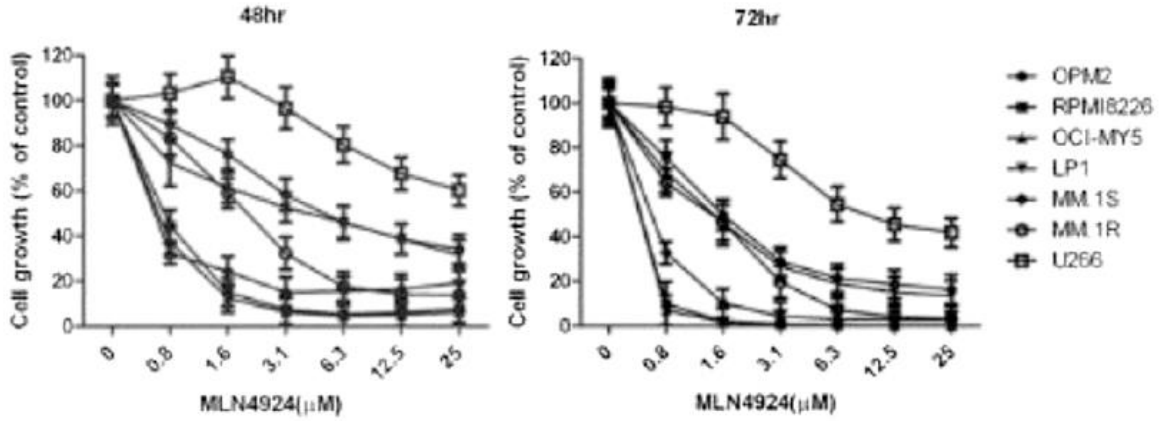

Figure 2: Human myeloma cell lines treated with MLN4924 (pevonedistat) for 48 or 72 hours (Gu *et al.*, 2014).

Preclinical data have also demonstrated increased cytotoxicity utilizing the combination of bortezomib and MLN4924 (pevonedistat), which is dependent upon REDD1 expression, subsequently leading to the down-regulation of the phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K)/ mechanistic target of rapamycin (mTOR) pathway. REDD1 is a CRL substrate that modulates mTOR pathway signaling. Using quantitative reverse transcription polymerase chain reaction (RT-qPCR), REDD1 mRNA levels have been shown to increase rapidly following exposure to MLN4924 (pevonedistat) in MM.1R myeloma cells (Figure 3) (Gu *et al.*, 2014).

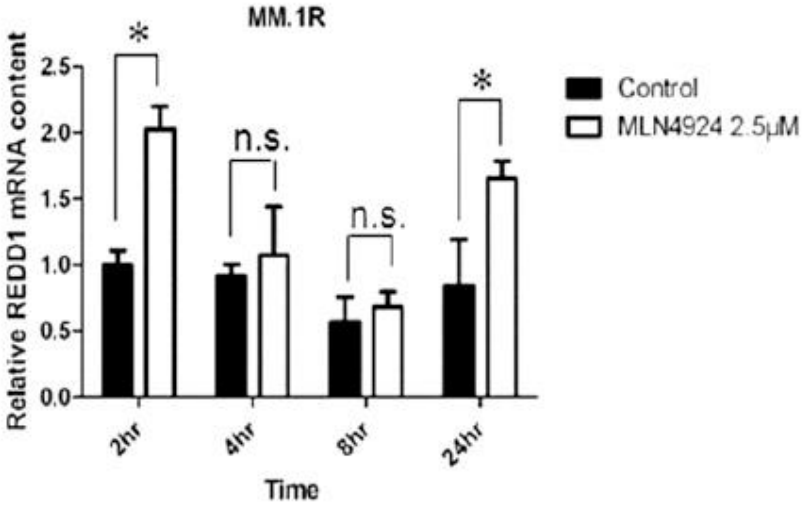

Figure 3: REDD1 mRNA levels measured by RT-qPCR in MM.1R cells treated with pevonedistat (MLN4924) at 2 hours, 4 hours, 8 hours, and 24 hours (Gu *et al.*, 2014).

Furthermore, when small interfering RNA (siRNA) is used to silence REDD1 expression, there is increased phosphorylation of mTOR, protein kinase B (AKT), eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1), and p70 ribosomal S6 kinase (p70S6K), proteins involved in the PI3K/mTOR pathway, suggesting suppression of this pathway is in fact dependent upon REDD1 (Figure 4) (Gu *et al.*, 2014). Bortezomib is known to affect mTOR signaling, and the

combination of MLN4924 (pevonedistat) with bortezomib not only results in increased cytotoxicity (Figure 5), but western blot analysis demonstrated marked suppression of the PI3K/mTOR pathway with the combination *versus* either agent alone in both myeloma cell lines and primary human myeloma cells (Figure 6). Again, silencing of REDD1 led to decreased growth inhibition when MLN4924 (pevonedistat) and bortezomib were used in combination, supporting the important role REDD1 plays both on the single-agent activity of MLN4924 (pevonedistat), and when used in combination with a PI.

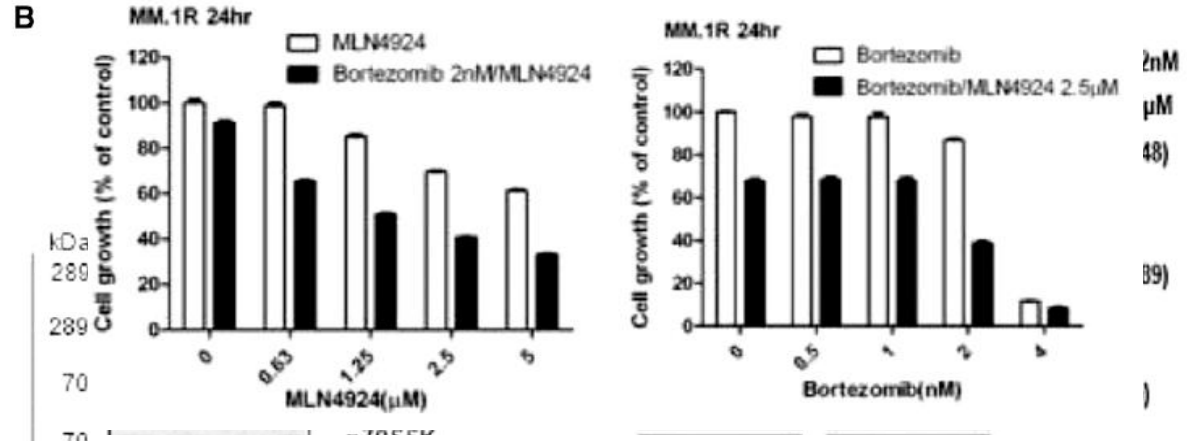

Figure 4: Cell viability of MM.1R cells treated with pevonedistat, bortezomib, or both (Gu *et al*., 2014).

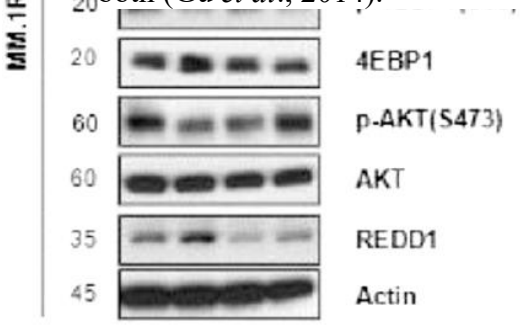

Figure 5: siRNA silencing of REDD1 leads to increased PI3K/mTOR pathway signaling (Gu *et al.*, 2014).

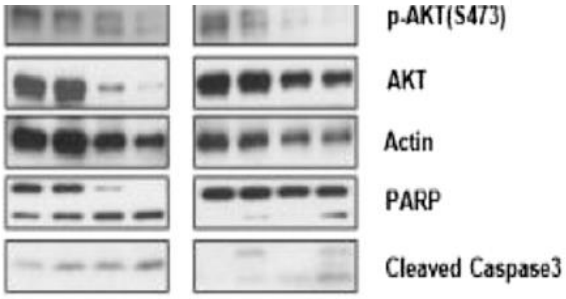

Figure 6: Primary human myeloma cells treated with pevonedistat, bortezomib, and the combination leading to increased inhibition of PI3K/mTOR pathway (Gu *et al*., 2014).

In a phase 1 study of MLN4924 (pevonedistat), Shah *et al*. treated 17 patients with RRMM after ≥2 prior lines of therapy (Shah *et al.*, 2016). MLN4924 (pevonedistat) was dosed on either Days 1, 2, 8, and 9 (Schedule A) or Days 1, 4, 8, and 11 (Schedule B) of 21-day cycles. The starting dose for both schedules was 25 mg/m^2 with dose escalations 1.33 times the prior dose. The predominant DLTs were febrile neutropenia, transaminitis, and muscle cramps on Schedule A, and thrombocytopenia on Schedule B. The MTD was 110 mg/m^2 on Schedule A and 196 mg/m^2 on Schedule B. The most common AEs included fatigue and nausea. Grade ≥3 AEs were limited to anemia (19%, Schedule A), neutropenia (12%, Schedule B), and pneumonia (12%, Schedule B). Thirteen of the seventeen patients, all of whom had previously been exposed to bortezomib, achieved SD.

The aim of this study is to improve upon the single-agent activity of MLN9708 (ixazomib) with the addition of MLN4924 (pevonedistat) without significant cumulative toxicity, as well as to assess which patient populations are more susceptible to this therapeutic approach (PI-sensitive *versus* PI-refractory). If antitumor activity is shown, the authors would consider moving forward in the identified population(s) of interest (PI-sensitive and/or PI-refractory) with a Simon's 2-stage design phase 2 study.

The hypotheses for this study are:

- The combination of MLN9708 (ixazomib) and MLN4924 (pevonedistat) will be synergistic resulting in improved efficacy in patients with RRMM compared to historical data of treatment with MLN9708 (ixazomib) alone.
- The MTD/RP2D of MLN4924 (pevonedistat) when administered in combination with MLN9708 (ixazomib) will be able to be determined.
- Collected correlative and PK and pharmacodynamics will recapitulate pre-clinical data.

2.4 Correlative Studies Background

2.4.1 MLN4924 (Pevonedistat) PK Profile

MLN4924 (pevonedistat) PK values will be obtained to assess dose-exposure-effect relationships with AEs, pharmacodynamic markers, and, potentially, response. The concentrations of MLN4924 (pevonedistat) that demonstrated activity with bortezomib *in vitro* (2.5 mcM or higher) are achievable with the doses to be utilized in this trial. The full metabolic fate of MLN4924 (pevonedistat) is still to be determined, and patient level variables that impact disposition are being globally investigated. Within this combination trial with MLN9708 (ixazomib), Cycle 1, Day 1 MLN4924 (pevonedistat) PK profiles will be obtained at each dose level for the purpose of relating exposure to clinical and pharmacodynamic outcomes, with the expectation that Day 1 exposures are equivalent to subsequent exposures due to prior data on clearance rates, known PK of MLN9708 (ixazomib), and weekly dosing interval.

2.4.2 *NQO1* and *SLC7A11* (NRF2 Target Genes) Expression

NAE activates the ubiquitin-like protein NEDD8 for conjugation to CRLs and, therefore, regulates the proteasomal destruction of CRL substrate proteins (Walker *et al*., 2011). NAE inhibition prevents degradation of CRL substrates (*e.g*., NRF2, CDT1), leading to their accumulation. To develop a pharmacodynamic assay, Walker *et al.* (2011) developed a RT-PCR-based assay using blood samples from multiple healthy volunteers that were treated *ex vivo* with a range of MLN4924 (pevonedistat) concentrations. Eight genes (including the NRF2-regulated genes *NQO1* and *SLC7A11*) displayed a robust induction (>3-fold) in whole blood. This assay is aimed at assessing whether MLN4924 (pevonedistat) target engagement, as measured by increased NRF2-regulated *NQO1* and *SLC7A11* gene expression in whole blood by RT-PCR, is a biomarker of MLN4924 (pevonedistat) activity.

2.4.3 MLN9708 (Ixazomib) Limited PK Profile

MLN9708 (ixazomib) PK sampling will be obtained on Days 1 and 15 in Cycles 1 and 3 to assess peak concentrations and accumulation effects. These values will be assessed in the context of MLN4924 (pevonedistat) PK, pharmacodynamic markers, response data, and AE data.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have RRMM with measurable disease, as defined by at least one of the following:

- Serum monoclonal protein ≥0.5 g/dL
- Urinary monoclonal protein excretion of ≥200 mg/24 hours
- Kappa or lambda light chain level ≥10 mg/dL with an abnormal free light chain ratio

3.1.2 At least two prior lines of therapy and all patients should have at least been exposed to a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 antibody.

- For proteasome-sensitive expansion cohort: Patients with MM who relapsed or are refractory to a prior line of therapy not including a proteasome inhibitor
- For proteasome-relapsed/refractory expansion cohort: Patients with MM who have relapsed after prior PI exposure or are PI-refractory, defined as nonresponsive to treatment or progresses within 60 days of last exposure to a PI

3.1.3 Age ≥18 years.

Because no dosing or AE data are currently available on the use of MLN4924 (pevonedistat) in combination with MLN9708 (ixazomib) in patients <18 years of age, and as this disease is exceptionally uncommon in this age group, children are excluded from this study.

3.1.4 Eastern Cooperative Oncology Group (ECOG) performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.5 Patients must have adequate organ and marrow function as defined below:

– Leukocytes	≥3,000/mcL
– Absolute Neutrophil Count	≥1,000/mcL
– Platelets	≥75,000/mcL
– Bilirubin	≤ institutional upper limit of normal (ULN). – Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5 × ULN
– AST(SGOT)/ALT(SGPT)	≤3.0 × institutional ULN
– CrCl by Cockcroft-Gault	≥30 mL/min

3.1.6 Known HIV positive patients who meet the following criteria will be considered eligible:

- CD 4 count >350 cells/mm^3
- Undetectable viral load

- Maintained on modern therapeutic regimens utilizing non-CYP-interactive agents (*e.g*. excluding ritonavir)
- No history of Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infections

3.1.7 The effects of MLN4924 (pevonedistat) and MLN9708 (ixazomib) on the developing human fetus are unknown. For this reason and because NAE inhibitory agents are known to be teratogenic, women of child-bearing potential and men must meet the following criteria:

Female patients who are:

- Postmenopausal for at least one year before the screening visit, OR
- Surgically sterile, OR
- If of childbearing potential, agree to practice 1 highly effective method and 1 additional (barrier) method of contraception, at the same time, from the time of signing the informed consent until 4 months after the last dose of the ixazomib and pevonedistat (female and male condoms should not be used together), or agree to abstain from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject (Periodic abstinence [*e.g*,, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Male patients, even if surgically sterilized, who:

- Agree to practice effective barrier contraception during the entire time enrolled on study through 4 months after completion of ixazomib and pevonedistat administration (female and male condoms should not be used together), OR
- Agree to abstain from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [*e.g*., calendar, ovulation, symptothermal, postovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

3.1.8 Ability to understand and the willingness to sign a written informed consent document. Participants with impaired decision-making capacity (IDMC) who have a legally-authorized representative (LAR) and/or family member available will also be eligible.

3.2 Exclusion Criteria

3.2.1 Diagnosed or treated for another malignancy within 2 years before randomization or previously diagnosed with another malignancy and have any evidence of residual disease. Patients with non-melanoma skin cancer or carcinoma *in situ* of any type are not

excluded if they have undergone resection.

3.2.2 Patients who are receiving any other investigational agents, within 30 days of the start of this trial and throughout the duration of this trial.

3.2.3 Patients with known central nervous system involvement should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other AEs.

3.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MLN4924 (pevonedistat) or MLN9708 (ixazomib) (including boron or boron-containing products).

3.2.5 Patients with uncontrolled intercurrent illness.

3.2.6 Pregnant women are excluded from this study because MLN4924 (pevonedistat) is an NAE inhibitory agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with MLN4924 (pevonedistat), breastfeeding should be discontinued if the mother is treated with MLN4924 (pevonedistat). These potential risks may also apply to the use of MLN9708 (ixazomib) in this study.

3.2.7 Major surgery within 14 days before the first dose of any study drug or a scheduled surgery during study period.

3.2.8 Patients with uncontrolled coagulopathy or bleeding disorder.

3.2.9 Known hepatic impairment as defined by known hepatic cirrhosis, hepatitis B surface antigen seropositive or known or suspected active hepatitis C infection

Note: Patients who have isolated positive hepatitis B core antibody (*i.e.*, in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load. Patients who have positive hepatitis C antibody may be included if they have an undetectable hepatitis C viral load.

3.2.10 Known cardiopulmonary disease defined as:

- Unstable angina;
- Congestive heart failure (New York Heart Association [NYHA] Class III or IV; see Appendix D);
- Myocardial infarction within 6 months prior to first dose (patients who had ischemic heart disease such as acute coronary syndrome [ACS], myocardial infarction, and/or revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll);
- Symptomatic cardiomyopathy
- Clinically significant arrhythmia:
    1. History of polymorphic ventricular fibrillation or torsade de pointes,

2. Permanent atrial fibrillation, defined as continuous atrial fibrillation for ≥6 months,
3. Persistent atrial fibrillation, defined as sustained atrial fibrillation lasting >7 days and/or requiring cardioversion in the 4 weeks before screening,
4. Grade 3 atrial fibrillation defined as symptomatic and incompletely controlled medically, or controlled with device (*e.g.*, pacemaker), or ablation in the past 6 months and
5. Patients with paroxysmal atrial fibrillation or Grade <3 atrial fibrillation for period of at least 6 months are permitted to enroll provided that their rate is controlled on a stable regimen.

- Clinically significant pulmonary hypertension requiring pharmacologic therapy

3.2.11 Uncontrolled high blood pressure (*i.e.*, systolic blood pressure >180 mmHg, diastolic blood pressure >95 mmHg).

3.2.12 Prolonged rate corrected QT (QTc) interval ≥500 msec, calculated according to institutional guidelines.

3.2.13 Left ventricular ejection fraction (LVEF) <50% as assessed by echocardiogram.

3.2.14 Known moderate to severe chronic obstructive pulmonary disease, interstitial lung disease, and pulmonary fibrosis.

3.2.15 Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 (ixazomib), including difficulty swallowing.

3.2.16 Peripheral neuropathy that is Grade ≥3, or Grade 2 with pain on clinical examination during the screening period.

3.2.17 Patients that have previously been treated with MLN9708 (ixazomib).

3.2.18 Systemic treatment, within 14 days before the first dose of MLN9708 (ixazomib), with strong CYP3A inducers (rifampin, rifapentine, rifabutin, ritonavir, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort. Clinically significant metabolic enzyme inducers are not permitted during this study.

3.2.19 Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the MLN9708 (ixazomib).

3.2.20 Female patients who intend to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

3.2.21 Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

3.3 Inclusion of Women and Minorities

National Institute of Health (NIH) policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the patients or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

All eligible patients regardless of sex/gender, race, or ethnicity will have the opportunity to enroll. The expected distribution of sex, race, and ethnicity will reflect the general population of our institution. Further details on planned distribution can be found in the table in Section 9.2.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (*i.e.*, clinical site staff requiring write access to Oncology Patient Enrollment Network (OPEN), Rave, or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR: MD, DO, or international equivalent,
- NPIVR: advanced practice providers (*e.g.*, NP or PA) or graduate level researchers (*e.g.*, PhD),
- AP: clinical site staff (*e.g.*, RN or CRA) with data entry access to CTSU applications (*e.g.*, Roster Update Management System [RUMS], OPEN, Rave,),
- Associate (A): other clinical site staff involved in the conduct of NCI-sponsored trials, and
- Associate Basic (AB): individuals (*e.g.*, pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster,

- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN,
- Act as the site-protocol Principal Investigator (PI) on the IRB approval, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

In addition, all investigators act as the Site-Protocol PI, consenting/treating/drug shipment, or as the CI on the DTL must be rostered at the enrolling site with a participating organization (*i.e.*, Alliance).

Additional information is located on the CTEP website at https://ctep.cancer.gov/investigatorResources/default.htm. For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Site Registration

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Sites participating with the NCI Central Institutional Review Board (NCI CIRB) must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by emailing the email address above or calling 1-888-651-CTSU (2878).

In addition, the Site-Protocol PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five criteria to complete processing of the IRB/REB approval record:

- Holds an Active CTEP status,
- Rostered at the site on the IRB/REB approval (*applies to US and Canadian sites only*) and on at least one participating roster,
- If using NCI CIRB, rostered on the NCI CIRB Signatory record,
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile, and
- Holds the appropriate CTEP registration type for the protocol.

Additional Requirements

Additional requirements to obtain an approved site registration status include:

- An active Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select LAO-MD017, and protocol number 10249,
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

4.2.2 Requirements For 10249 Site Registration

- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
  - This training will need to be completed before the first patient enrollment at a given site.
  - Please contact STS Support at Theradex for the training (STS.Support@theradex.com, Theradex phone: 609-799-7580).

4.2.3 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal, log on to the CTSU members' website → Regulatory → Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal

should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

4.2.4 Checking Site Registration Status

You can verify your site's registration status on the members' side of the CTSU website.

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *Site Registration*
- Enter your 5-character CTEP Institution Code and click on Go

Note: The status shown only reflects institutional compliance with site registration requirements as outlined above. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

4.3 Patient Registration

4.3.1 OPEN / IWRS

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the Lead Protocol Organization (LPOs) registration/randomization systems or Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account.
- To perform enrollments or request slot reservations: Be on an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- Have an approved site registration for a protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

Special Instructions for Patient Enrollment

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

4.3.2 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Theradex has developed a Slot Reservations and Cohort Management User Guide, which is available on the Theradex website: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. This link to the Theradex website is also on the CTSU website OPEN tab. For questions about the use of IWRS for slot reservations, contact the Theradex Helpdesk at 609-619-7862 or Theradex main number 609-799-7580; CTMSSupport@theradex.com.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 30 days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
1	MLN4924 (pevonedistat) PK profile	LC/MS/MS	Integrated PK analysis	M	Cycle 1, Day 1 pre-dose, and at the following time points after initiation of infusion: 0.5 hr ±10 min, 1 hr ±10 min, 2 hrs ±10 min, 2.5 hrs ±10 min, 5 hrs, ±30 min, 8 hrs ±45 min, and 21 hrs ±2 hrsin the dose escalation portion only	Plasma	3 mL in EDTA tubes at each time point	QPS, LLC
2	*NQO1* and *SLC7A11* (NRF2 target genes)	qRT-PCR	Integrated Hypothesis generation to develop response predictors	M	Pre-treatment, and 4 hours post-MLN4924 (pevonedistat) completion on C1D1	Blood	2.5 mL	Asuragen Deepa Eveleigh develeigh@asuragen.com

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
3	MLN9708 (ixazomib) limited PK profile	LC/MS/MS	Integrated PK analysis	M	C1D1, C1D15, C3D1, and C3D15 at the following timepoints: pre-dose and 1 hr ±10 min after dosing in the dose escalation portion only	Plasma	3 mL at each time point	QPS, LLC
2	*ATF3, B2M, GCLM, GSR, MAG1, RPLP0, SRXN1, TXNRD1,* and *UBC*	RT-PCR	Exploratory Hypothesis generation to develop response predictors	M	Pre-treatment and 4 hours post-MLN4924 (pevonedistat) completion on C1D1	Blood	N/A (Same collection as *NQO1* and *SLC7A11* Biomarker)	Asuragen Deepa Eveleigh develeigh@asuragen.com

M = Mandatory, PK = Pharmacokinetics, LC/MS/MS = Liquid chromatography/tandem mass spectrometry, EDTA = Ethylenediaminetetraacetic acid, PBMC = Peripheral blood mononuclear cell, Na = Sodium, NQO1 = NAD(P)H dehydrogenase (quinone) 1, SLC7A11 = Cystine/glutamate transporter, NRF2 = Nuclear factor (erythroid-derived 2)-like 2, qRT-PCR = Quantitative reverse transcription polymerase chain reaction

Specimen Collection Schedule

Specimen Type	Baseline (Pre-treatment)	Cycle 1, Day 1	Cycle 1, Day 15	Cycle 3, Day 1	Cycle 3, Day 15	End of Study
Plasma[c]		X[a,b]	X[b]	X[b]	X[b]	
Blood (PBMC isolation)	X					
Blood	X					X

PMBC = Peripheral blood mononuclear cell
a: Plasma for MLN4924 (pevonedistat) and MLN9708 (ixazomib) PK profiles. Time points to be collected for MLN9708 (ixazomib) and MLN4924 (pevonedistat) PK profiles are: pre-dose and 1 hr ±10 min after initiation of infusion. Additional time points to be collected for only MLN4924 (pevonedistat) PK profile are: 0.5 hr ±10 min, 2 hr ±10 min, 2.5 hr ±10 min, 5 hrs ±30 min, 8 hr ±45 min, and 21 hrs ±2 hrs after initiation of infusion.
b: Plasma for MLN9708 (ixazomib) PK profile. Time points to be collected are: pre-dose and 1 hr ±10 min after initiation of infusion.
c: Plasma will only be collected during the dose escalation phase.

5.2 Integrated Correlative Studies

5.2.1 MLN4924 (Pevonedistat) PK Profile

5.2.1.1 Collection of Specimen(s)

Blood samples (3 mL) will be collected in chilled lavender top K2EDTA Vacutainer tube for plasma analysis on Cycle 1, Day 1 pre-dose and at the following time points after initiation of infusion: pre-dose, 0.5 hour ±10 min, 1 hour ±10 min, 2 hours ±10 min, 2.5 hours ±10 min, 5 hours, ±30 min, 8 hours ±45 min, and 21 hours ±2 hours. This study will only be performed during the dose escalation portion.

Legibly write the subject's initials and subject identification number clearly using a blue or black pen only (no markers) on the blood collection tubes. Cryovial labels must include the protocol number, subject identification number, and the sample identification code shown below. The (nominal time) may be the scheduled visit and/or time point.

- a. Plasma PK Pevo (nominal time) Set1
- b. Plasma PK Pevo (nominal time) Set2

5.2.1.2 Handling of Specimens(s)

1. Gently invert the Vacutainer 8 to 10 times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
2. Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 × g (RCF) at approximately 4°C in a refrigerated centrifuge. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
3. Immediately following centrifugation, gently remove plasma from the packed cells and transfer into 2 appropriately labeled 2.0 mL cryogenic vials. To ensure a more homogeneous sample, transfer all plasma into one cryovial. From there, split the plasma evenly between the 2 aliquots. A minimum of 0.6 mL needs to be obtained for each aliquot.
4. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70°C or lower. If a -70°C freezer is not available, freeze and store samples at -20°C. No more than 45 minutes will elapse between blood collection and freezing the plasma sample.
5. Store samples frozen at approximately -70°C or lower until shipment. If a -70°C freezer is not available, samples can be stored in a -20°C freezer for up to 30 days.

5.2.1.3 Shipping of Specimen(s)

1. All samples to be shipped to below address.
2. Primary and backups of same sample should **not** be shipped together.
3. Each shipment should include a Sample Inventory.

4. Please notify QPS of the shipment with sample inventory copy via email (email address below) ahead of time, or at the latest on the day of shipment.
5. Samples will be packed in styrofoam shipping containers with a sufficient amount of dry ice to maintain frozen conditions for at least 72 hours (3 days), or up to the expected delivery date, whichever is longer.

QPS Sample Receipt Address:

Attn: Sample Coordination Team
QPS, LLC
3 Innovation Way
Suite 240
Newark, DE, 19711
Phone: +1 302 369 5120
Email: sample@qps.com

5.2.1.4 Site(s) Performing Correlative Study

QPS, LLC will analyze plasma for MLN4924 (pevonedistat) and MLN9708 (ixazomib) PK.

5.2.2 NQO1 and SLC7A11 (NRF2 Target Genes) Expression

5.2.2.1 Collection of Specimen(s)

Blood (2.5 mL) will be collected prior to treatment and 4 hours after MLN4924 (pevonedistat) completion on Cycle 1, Day 1.

Instructions for Processing Samples

1. Ensure that the PAXgene Blood RNA Tube is at room temperature prior to use and properly labeled with the protocol number, whether pre- or post-study, and the patient study ID.
2. If the PAXgene Blood RNA Tube is the only tube to be drawn, a small amount of blood should be drawn into a discard tube prior to drawing blood into the PAXgene Blood RNA Tube. Otherwise, the PAXgene Blood RNA Tube should be the last tube drawn in the phlebotomy procedure.
3. Using a BD Vacutainer Safety-Lok Blood Collection Set (or equivalent), collect 2.5 mL of blood into the PAXgene Blood RNA Tube using the local institution's recommended standard procedure for phlebotomy. Samples from a central venous catheter are also acceptable and should be obtained using the local institution's recommended procedures. Note that the PAXgene tube is a standard sized 10 mL blood draw tube with 7.5 mL of RNA stabilizing agent in it, so 2.5 mL of blood is drawn in, for a total of 10 mL.
4. Hold the PAXgene Blood RNA Tube vertically and below the patient's arm during blood collection.
5. Allow at least 10 seconds for a complete blood draw to take place. Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.

5.2.2.2 Handling of Specimens(s)

1. Gently invert the PAXgene Blood RNA Tube 8-10 times.
2. Freeze PAXgene Blood RNA Tubes at -20°C until ready to ship.

5.2.2.3 Shipping of Specimen(s)

The PAXgene tubes can be batched and shipped on dry ice same day or overnight to Asuragen. Please reference either the trial ID or Asuragen project code on the package and any shipping manifest provided. Shipping manifests with detailed sample information should be sent to: develeigh@asuragen.com.

Ship samples to:

Asuragen
2150 Woodward St., Suite 100
Austin, TX 78744

5.2.2.4 Site(s) Performing Correlative Study

The test will be performed at Asuragen.

5.2.3 MLN9708 (ixazomib) Limited PK Profile

5.2.3.1 Collection of Specimen(s)

Blood samples (3 mL) will be collected in appropriately labeled chilled lavender top K2EDTA Vacutainer tube for plasma analysis on Cycle 1, Day 1; Cycle 1, Day 15; Cycle 3, Day 1; and Cycle 3, Day 15 at the following time points: pre-dose and 1 hour ±10 minutes after dosing. This study will only be performed during the dose escalation portion.

5.2.3.2 Handling of Specimens(s)

1. Immediately mix the blood with the anticoagulant by gently inverting the tube 8-10 times to thoroughly mix the blood with the anticoagulant (do not shake), and immediately place the blood collection tube on wet ice
   • NOTE: Wet ice is defined as a mixture of ice and water.
2. Within 10 minutes of blood collection, centrifuge the blood samples for 10 minutes at 1600 × g at 4°C in a refrigerated centrifuge.
3. Immediately following centrifugation, gently remove the plasma and aliquot into two pre-labeled transfer vials filled with lyophilized citric acid. Each aliquot should contain 0.5 mL of plasma.
   • NOTE: If <0.5 mL plasma is obtained post centrifugation, do not process or store split1 or split2, record split1: ISV (Insufficient Sample Volume), split2: ISV.
4. Securely cap the tube and freeze the samples immediately at -70°C.
5. No more than 30 minutes should elapse between blood collection and freezing the plasma samples. Keep samples frozen at -70°C or lower until shipment.

5.2.3.3 Shipping of Specimen(s)

6. All samples to be shipped to below address.
7. Primary and backups of same sample should not be shipped together.
8. Each shipment should include a Sample Inventory.
9. Please notify QPS of the shipment with sample inventory copy via email (email address below) ahead of time, or at the latest on the day of shipment.
10. Samples will be packed in styrofoam shipping containers with a sufficient amount of dry ice to maintain frozen conditions for at least 72 hours (3 days), or up to the expected delivery date, whichever is longer.

QPS Sample Receipt Address:

Attn: Sample Coordination Team
QPS, LLC
3 Innovation Way
Suite 240
Newark, DE, 19711
Phone: +1 302 369 5120
Email: sample@qps.com

5.2.3.4 Site(s) Performing Correlative Study

QPS, LLC will analyze plasma for MLN4924 (pevonedistat) and MLN9708 (ixazomib) PK.

5.3 Exploratory Correlative Studies

5.3.1 *ATF3*, *B2M*, *GCLM*, *GSR*, *MAG1*, *RPLP0*, *SRXN1*, *TXNRD1*, and *UBC*

5.3.1.1 Collection of Specimen(s)

This study will use the sample collected in Section 5.2.3.1.

5.3.1.2 Handling of Specimens(s)

See Section 5.2.3.1 for information on the handling of this specimen.

5.3.1.3 Shipping of Specimen(s)

See Section 5.2.3.3 for information on the shipping of this specimen.

5.3.1.4 Site(s) Performing Correlative Study

This study will be performed by Asuragen.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Reported AEs and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

This is a phase 1 clinical trial of MLN9708 (ixazomib) in combination with MLN4924 (pevonedistat) in RRMM patients. This clinical trial will use a 3+3 dose escalation design to determine the MTD for the combination of MLN9708 (ixazomib) and MLN4924 (pevonedistat) to target a DLT rate of less than 33% in myeloma patients regardless of status of PI sensitivity. MLN9708 (ixazomib) will be given on Days 1, 8, and 15 of a 28-day cycle. MLN4924 (pevonedistat) will be given concurrently on Days 1, 8, and 15 of a 28-day cycle. The trial will start from dose level 1. If no patient experiences a DLT in a 3-patient cohort at a given dose level, then the dose will be escalated to the next higher level. If a DLT occurs in 1 of 3 patients at a dose level, the cohort will be expanded to 6 patients. If the incidence of DLT among those 6 patients is 1 in 6, then the next cohort of 3 patients is treated at the next higher dose. If 2 or more patients experience a DLT in a 3-patient or 6-patient cohort at a given dose level, then the MTD has been exceeded, dose escalation will be stopped, and up to 3 additional patients will be enrolled at the next lower dose (unless 6 patients have already been treated at that prior dose). The MTD will be the highest dose at which 1 or fewer of six patients experience a DLT. In the expansion phase, a total of 24 patients will be enrolled at the MTD of MLN4924 (pevonedistat) defined in the dose escalation phase in 2 cohorts: PI-sensitive and PI-refractory. Refractoriness will be defined as per the 2011 International Myeloma Working Group (IMWG) definition, disease that is nonresponsive to treatment or progresses within 60 days of last exposure to a PI.

Dose Escalation Schedule		
Dose Level	**Dose**	
	MLN9708 (Ixazomib) PO QD on Days 1, 8, and 15	**MLN4924 (Pevonedistat) IV on days 1, 8, and 15***
Level -2	3 mg	15 mg/m^2
Level -1	3 or 4 mg[#]	15 or 20 mg/m^{2}[#]
Level 1	4 mg	20 mg/m^2
Level 2	4 mg	40 mg/m^2
Level 3	4 mg	60 mg/m^2
Level 4	4 mg	80 mg/m^2
Level 5	4 mg	100 mg/m^2
PO = by mouth, QD = once daily, IV = intravenous [#] Agent attribution for DLT will dictate which drug is dose reduced for dose level -1. No dose reduction below 3 mg for MLN9708 (ixazomib) and 15 mg/m^2 for MLN4924 (pevonedistat)		

will be allowed. Should a DLT occur attributable to either agent at the lowest dose level, the trial will be stopped.
* Dose rounding is allowed as per institutional guidelines.

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
MLN9708 (Ixazomib)	N/A	**	PO (To be given concurrently with MLN4924 [Pevonedistat])	Days 1, 8, and 15	28 days (4 weeks)
MLN4924 (Pevonedistat)	N/A	**	IV (Infuse over 60 minutes [±10 minutes])	Days 1, 8, and 15	
PO = by mouth, IV = intravenous ***Doses as appropriate for assigned dose level.*					

6.1.1 MLN9708 (Ixazomib)

Patients should be instructed to swallow MLN9708 (ixazomib) capsules whole, with water, and not to break, chew, or open the capsules. MLN9708 (ixazomib) should be taken on an empty stomach (no food or drink) at least 1 hour before or at least 2 hours after food. Each capsule should be swallowed separately with water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules. MLN9708 (ixazomib) should be given concurrently with MLN4924 (pevonedistat).

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.

Fluid deficit should be corrected before initiation of treatment and during treatment.

Prophylaxis against risk of reactivation of herpes infection: Investigators should consider the use of antiviral prophylaxis for patients being treated with MLN9708 (ixazomib), as patients may be at an increased risk of infection, including reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir, valacyclovir, or other antivirals may be initiated as clinically indicated. Other antivirals are also acceptable.

6.1.2 MLN4924 (Pevonedistat)

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

If MLN4924 (pevonedistat) dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained. In each cycle, a maximum of 3 doses of MLN4924 (pevonedistat) should not be exceeded.

The dose will be calculated based on BSA using actual body weight. Re-calculate dose if there is a change in body weight of ≥5%.

Infuse over 60 minutes (±10 minutes) through central or peripheral venous access. The IV infusion can be slowed or stopped and restarted for any associated infusion-related reactions. The total time from the IV preparation to end of IV infusion must not exceed 6 hours. MLN4924 (pevonedistat) should be given concurrently with MLN9708 (ixazomib).

6.2 Definition of Dose-Limiting Toxicity

DLT will be defined as any of the following events that are considered by the investigator to be related to therapy with MLN4924 (pevonedistat):

- Grade 3 or greater prothrombin time (PT) or activated partial thromboplastin time (aPTT) elevation in the absence of anticoagulation therapy.
- Grade 2 or greater elevation of the PT or aPTT that is associated with clinically significant bleeding (CNS, GI, *etc*.).
- Grade 3 or greater nausea and/or emesis despite use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-hydroxytryptamine 3 serotonin receptor antagonist given in standard doses and according to standard schedules.
- Grade 3 or greater diarrhea that occurs despite maximal supportive therapy.
- Grade 3 arthralgia/myalgia despite the use of optimal analgesia.
- Any other Grade 3 or greater non-hematologic toxicities (*e.g*. nausea, vomiting, diarrhea, *etc*.) despite optimal medical management, with the following exception:
    - Grade 3 hypophosphatemia
- Persistent elevations of one of the 2 transaminases or bilirubin above Grade 2 beyond 2 days between doses.
- Other MLN4924 (pevonedistat)-related non-hematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require a dose reduction or discontinuation of therapy with MLN4924 (pevonedistat).
- A delay in the initiation of Cycle 2 due to a lack of adequate recovery from treatment-related toxicity (recovery to Grade ≤1 or to patient's baseline values):
    - Of more than 4 weeks due to hematologic toxicity believed not related to leukemic infiltration. Bone marrow evaluation may be required.
    - Of more than 2 weeks due to nonhematologic toxicities.
- Grade 3 fatigue >1 week
- Grade ≥3 electrolyte abnormalities Grade 4 neutropenia (ANC <500 cells/mm^3) lasting more than 7 consecutive days.

- Grade 3 neutropenia with fever and/or infection, where fever is defined as an oral temperature ≥38.5°C.
- Grade 4 thrombocytopenia (platelets <25,000/mm^3 but >10,000/mm^3) lasting more than 7 consecutive days.
- Grade 3 thrombocytopenia with bleeding.
- A platelet count <10,000/mm^3 at any time.
- Grade 4 anemia not attributable to underlying disease process.

Grade 3 events lasting <1 week will not be considered a DLT. Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment related- toxicities.

Management and dose modifications associated with the above AEs are outlined in Section 7.

Dose escalation will proceed within each cohort according to the following scheme. DLT is defined above.

Number of Patients with DLT at a Given Dose Level	**Escalation Decision Rule**
0 out of 3	Enter 3 patients at the next dose level.
≥2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤1 out of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

6.3 Dose Expansion Cohorts:

Once the RP2D is reached, an additional 24 patients will be treated at this dose. For the

expansion cohort, patients will continue to be monitored for occurrence of DLTs as in the table below. If the number of DLTs warrant stopping of the trial for toxicity, the Principal Investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module. All participating sites are expected to notify the Principal Investigator when a DLT has occurred.

The pre-stopping rule in the Table below is generated based on the cumulative distribution function (CDF) of the binomial distribution, given the number of successes, the number of trials, and the probability of a successful outcome occurring. The trial will be pre-stopped when the CDF is greater than 95% based on 33% DLT.

Total number of treated patients	Number of DLTs to stop the trial for toxicity
3	≥2
4	≥3
5	≥3
6	≥4
7	≥4
8	≥5
9	≥5
10	≥6
11	≥6
12	≥7
13	≥7
14	≥8
15	≥8
16	≥8
17	≥9
18	≥9
19	≥10
20	≥10
21	≥11
22	≥11
23	≥11
24	≥12

6.4 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of MLN9708 (ixazomib) and/or MLN4924 (pevonedistat) with other concomitantly administered drugs that require CYP450 enzyme and transport protein, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Principal Investigator should be alerted if the patient is taking drugs that are moderate/strong inducers of CYP3A4, or moderate/strong

inhibitors/inducers of P-gp, BCRP, and MRP2. The study team should check a frequently-updated medical reference for a list of drugs to avoid or minimize use of. Appendix B and Appendix C (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

6.4.1 MLN9708 (Ixazomib)

6.4.1.1 Excluded Concomitant Medications and Procedures

Strong CYP3A4/5 inducers decrease MLN9708 (ixazomib) exposure; thus, avoid concomitant use of strong CYP3A4/5 inducers (*e.g.*, rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital, and St. John's Wort) with MLN9708 (ixazomib).

The following medicinal products and procedures are prohibited during the study:

- St. John's Wort.
- Any antineoplastic treatment with activity against MM, other than study drugs.
- Radiation therapy (note that, in general, the requirement for local radiation therapy indicates disease progression).
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days prior to study drug dosing for any dosing day.
- Acetaminophen and acetaminophen-containing products 2 g per day are not allowed during MLN4924 (pevonedistat) and MLN9708 (ixazomib) treatment schedules.

Nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function.

6.4.1.2 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator and as per institutional policy and guidelines.
- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. IV fluids should be given to prevent volume depletion.
- Growth factors (*e.g.*, granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], and recombinant erythropoietin) are permitted. Their use should follow published guidelines and/or institutional practice; however, alternative usage may be reviewed with the study sponsor. Erythropoietin will be allowed in this study. Its use should follow published guidelines and/or institutional practice.
- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.
- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Patients who experience worsening neuropathy from baseline may be observed for recovery and have dose reductions/delays as indicated in the protocol, and any supportive

therapy or intervention may be initiated as appropriate at the discretion of the investigator.
- Supportive measures consistent with optimal patient care may be given throughout the study.

6.4.2 MLN4924 (Pevonedistat)

MLN4924 (pevonedistat) is metabolized mainly by CYP3A4 and may be affected by drugs that are moderate or strong inducers of CYP3A4. MLN4924 (pevonedistat) (*in vitro*) is also a substrate of P-gp, BCRP, and MRP2. The tables below list concomitant medications that are permitted and excluded, and those whose use should be avoided while taking MLN4924 (pevonedistat).

6.4.2.1 Excluded Concomitant Medications and Procedures

Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	For patients in the dose-escalation phase of a clinical study, agents such as acetaminophen and acetaminophen-containing products should not be administered 24 hours before, on the day of, and 24 hours after dosing with pevonedistat. For patients not in dose escalation, agents such as acetaminophen and acetaminophen-containing compounds may be used judiciously and should not exceed a dose of 2 g of acetaminophen in a 24-hour period.
Systemic antineoplastic therapy, except for hydroxyurea	Hydroxyurea dosing during the study treatment phase may be adjusted to control the level of circulating blast counts to no lower than 10,000/mcL while on study treatment. The dosing of hydroxyurea and changes to dosing of hydroxyurea must be recorded.
Clinically significant metabolic enzyme inducers	Exclude carbamazepine, phenytoin, phenobarbital, primidone, rifabutin, rifampin, ritonavir, rifapentine and St. John's Wort.
Known BCRP inhibitors (*i.e.*, cyclosporine)	Excluded **but limited use is permitted only if clinically necessary and no suitable alternative exists.** The patient may receive the BCRP inhibitor from 24 hours after the last MLN4924 (pevonedistat) dose until 72 hours before the next MLN4924 (pevonedistat) dose. For example, if a patient receives MLN4924 (pevonedistat) on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the BCRP inhibitor may be administered from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle.
Any investigational agent other than MLN4924 (pevonedistat)	For example, androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag (Promacta), or romiplostim (Nplate) are excluded.

BCRP=breast cancer resistance protein

6.4.2.2 Permitted Concomitant Medications and Procedures

Concomitant Medications and Procedures Permitted During the Study

Therapy	Comment
Anti-platelet agents (*e.g.*, aspirin, clopidogrel) and anticoagulants	May be used in patients who have controlled coagulopathy at baseline, as well as those who develop a coagulopathy on study. Note that patients with active uncontrolled coagulopathy are excluded from enrollment.
Myeloid growth factors (*e.g.*, G-CSF, GM-CSF)	In general, the use of myeloid growth factors is discouraged and should be restricted. For patients in CR, CRi, or marrow CR, growth factors may be used in specific circumstances after discussion with the project clinician or designee. Use of growth factors may also be used in patients with Grade 3 or Grade 4 febrile neutropenia after discussion and agreement with the project clinician or designee. Additionally, to avoid dose delays, patients who experience Grade 4 neutropenia (ANC <500/mcL) with or without fever may receive granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) between days 28-42 days of azacitidine monotherapy or combination after discussion and agreement with the sponsor investigator (or designee). Patients who receive myeloid growth factors will not be included in assessment of neutrophil response.
Platelet transfusion	Permitted as medically necessary per institutional guidelines (*e.g.*, for platelets <10,000/mcL in the absence of clinical bleeding).
Red blood cell transfusion	To be considered for all patients with anemia, especially those with hemoglobin values ≤8 g/dL.

G-CSF=granulocyte colony-stimulating factor, GM-CSF=granulocyte macrophage colony-stimulating factor, CR=complete response, CRi=complete remission with incomplete blood count recovery, ANC=absolute neutrophil count.

6.5 Duration of Therapy

In the absence of treatment delays due to AE(s), treatment may continue until one of the following criteria applies:

- Disease progression as defined by the IMWG response criteria:
  - ≥25% increase or absolute increase ≥0.5 g/dL in serum M-protein.
  - ≥25% increase or absolute increase ≥200 mg/24 hours in urine M-protein.
  - For patients without measurable M-protein in the serum or urine, ≥25% increase in the kappa to lambda free light chain (FLC) ratio or an absolute increase >10 mg/dL.
  - For patient without measurable M-protein or involved FLC, ≥25% increase in bone marrow plasma cell percentage or an absolute increase must be ≥10%.
  - ≥50% increase in the size or development of new bone lesions or soft tissue plasmacytomas.

  Or one of the following attributable to underlying myeloma: serum calcium >11.5 mg/dL, decrease in hemoglobin of ≥2 g/dL, rise in serum creatinine ≥2 mg/dL, or hyperviscosity.

- Intercurrent illness that prevents further administration of treatment

- Unacceptable AE(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent
- Initiation of hematopoietic stem cell transplant
- Subsequent anti-cancer therapy
- The patient loses the capacity to freely consent to participate in the study due to psychiatric illness, incarceration, or other reasons.

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the Case Report Form (CRF).

6.6 Premature termination of the study

This study may be suspended or prematurely terminated if there is sufficient cause. Written notification, documenting the reason for study suspension or termination will be provided by the suspending or terminating party to the investigator, funding agency, the IND sponsor, and regulatory authorities. If the study is prematurely terminated or suspended, the PI will promptly inform the IRB and will provide the reason(s) for the termination or suspension.

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

- Determination of unexpected, significant, or unacceptable risk to participants

- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

6.7 Duration of Follow Up

Patients will be followed every 2-3 months for 2 years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable AE(s) will be followed until resolution or stabilization of the AE.

7. DOSING DELAYS/DOSE MODIFICATIONS

Dose Escalation Schedule		
Dose Level	**Dose**	
	MLN9708 (Ixazomib) PO QD on Days 1, 8, and 15	**MLN4924 (Pevonedistat) IV on days 1, 8, and 15**
Level -2	3 mg	15 mg/m^2
Level -1	3 or 4 mg[#]	15 or 20 mg/m$^{2[\#]}$
Level 1	4 mg	20 mg/m^2
Level 2	4 mg	40 mg/m^2
Level 3	4 mg	60 mg/m^2
Level 4	4 mg	80 mg/m^2
Level 5	4 mg	100 mg/m^2
PO = by mouth, QD = once daily, IV = intravenous		

[#]Agent attribution for DLT will dictate which drug is dose reduced for dose level -1. No dose reduction below 3 mg for MLN9708 (ixazomib) and 15 mg/m^2 for MLN4924 (pevonedistat) will be allowed. Should a DLT occur attributable to either agent at the lowest dose level, the trial will be stopped.

7.1 Criteria for Retreatment and Dose Delays

7.1.1 MLN9708 (Ixazomib)

MLN9708 (ixazomib) dose modifications are permitted on this study according to the dose modifications below. Once MLN9708 (ixazomib) is reduced for any toxicity, the dose may not be re-escalated.

Treatment with MLN9708 (ixazomib) will use a cycle length of 28 days. For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥1,000/mcL.
- Platelet count must be ≥75,000/mcL.
- All other non-hematologic toxicity (except for alopecia) must have resolved to Grade ≤1 or to the patient's baseline condition.

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re-evaluate. The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the Principal Investigator.

For dosing recommendations upon recovery, refer to Sections 7.2 and 7.3.

7.1.2 MLN4924 (Pevonedistat)

7.1.2.1 Retreatment within a Cycle

If dosing of either drug is delayed for safety reasons, retreatment may be resumed upon resolution of the safety condition. For MLN4924 (pevonedistat), a minimum of one full calendar day between any two doses should be maintained. A maximum of three doses of MLN4924 (pevonedistat) per cycle should not be exceeded.

If dosing is interrupted within a cycle because of drug-related toxicity, and if the sponsor investigator (or designee) agrees that it is in the patient's interest to continue therapy with the study drug(s), then after recovery of the toxicity or toxicities in question to Grade ≤1 or to the patient's baseline values, the dose of study drug may be reduced in the next cycle. For toxicity not related to drug (*e.g.*, disease-related toxicity), although a similar dose reduction is permitted, in general it is discouraged. If the reduced dose is well tolerated and the toxicity leading to dose reduction was Grade ≤3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor investigator (or designee).

7.1.2.2 Initiation of a New Cycle

Treatment with study drugs will be repeated every cycle. For therapy to resume, toxicity considered related to treatment with study drugs must have resolved to Grade ≤1, to the patient's baseline values, or to a level considered acceptable by the sponsor investigator.

If a patient fails to meet the criteria for retreatment, initiation of the next cycle of treatment may be delayed for up to 2 weeks. At the end of that time, the patient should be reevaluated to determine whether the criteria for retreatment have been met. A dose reduction would be triggered if treatment is delayed for >2 weeks because of incomplete recovery from treatment related toxicity. If the reduced dose is well tolerated and the toxicity leading to dose reduction was Grade ≤3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the sponsor investigator (or designee).

For toxicity not related to drug (*e.g.*, disease-related toxicity), although a similar dose reduction is permitted, in general it is discouraged. If the dose is well tolerated and the toxicity leading to dose reduction was Grade ≤3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle.

For hematologic toxicity, a delay in the initiation of a cycle by 3 weeks or greater because of lack of recovery from treatment-related hematologic toxicity (resolved to Grade ≤1, to patient's baseline values, or to a level considered acceptable by the sponsor investigator) that is not related to leukemic infiltration will trigger discontinuation of treatment. If indicated, bone marrow evaluation will be performed to establish whether continued myelosuppression is related to persistent or progressing leukemic infiltration. The MLN4924 (pevonedistat) dose should be reduced by at least one dose level.

7.2 Dose Modifications for Hematologic Toxicities

7.2.1 MLN9708 (Ixazomib)

The following tables provide AE management and MLN9708 (ixazomib) dose modification recommendations for hematologic toxicities.

MLN9708 (Ixazomib) Dose Adjustments for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count ≤30 × 10^9/L or ANC ≤0.50 × 10^9/L on an MLN9708 (ixazomib) dosing day (other than Day 1)	• MLN9708 (ixazomib) dose should be withheld. • CBC with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values (see Section 7.1.1) on at least 2 occasions. • Upon recovery, MLN9708 (ixazomib) may be reinitiated with 1 dose level reduction.
Dose Modifications for Subsequent Treatment Cycles	
• Delay of >2 weeks in the start of a subsequent cycle due to lack of toxicity recovery as defined above • ANC < 1.0 × 10^9/L, platelet count < 75 × 10^9/L	• Hold MLN9708 (ixazomib) until resolution as per criteria Section 7.1.1. • Upon recovery, reduce MLN9708 (ixazomib) 1 dose level. • The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the Principal Investigator.
Dose Modifications for Subsequent Treatment Cycles	
• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recover in time for the start of the next cycle: o If dose was reduced within the cycle, start the next cycle at that same dose. o If due to toxicity timing, *i.e.*, after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce MLN9708 (ixazomib) by 1 dose level at the start of that cycle. o Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

ANC: absolute neutrophil count; CBC: complete blood count.

7.2.2 MLN4924 (Pevonedistat)

It is not anticipated that pevonedistat dose modifications would be necessary due to myelosuppression. However, if clinically indicated in the opinion of the investigator, the

MLN4924 (pevonedistat) dose may be reduced one dose level. The MLN4924 (pevonedistat) dose may be re-escalated at the next cycle, if the toxicity has recovered to Grade ≤1 or the patient's baseline.

7.3 Dose Modifications for Nonhematologic Toxicities

7.3.1 MLN9708 (Ixazomib)

MLN9708 (Ixazomib) Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)*	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold study drug until resolution to Grade ≤1 or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental ADL
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold study drug until resolution to Grade ≤1 or baseline • Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 2 Rash	• Symptomatic recommendations as per Section 7.3.1.3	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Grade 3 non-hematologic toxicity judged to be related to study drug	• Hold study drug until resolution to Grade <1 or baseline	Symptomatic recommendations noted later in this Section.
If not recovered to Grade <1 or baseline within 4 weeks	• Reduce study drug 1 to next lower dose upon return to Grade <1 or baseline	

MLN9708 (Ixazomib) Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)*	Action on Study Drug	Further Considerations
Subsequent recurrence Grade 3 that does not recover to Grade <1 or baseline within 4 weeks	• Hold study drug until resolution to Grade <1 or baseline • Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 non-hematologic toxicities judged to be related to study drug	• Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the patient is obtaining a clinical benefit

*Grade is defined according to the Common Terminology Criteria for Adverse Events (CTCAE).
ADL = activities of daily living

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with MLN9708 (ixazomib) treatment. Management guidelines regarding these events are outlined below.

7.3.1.1 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.

7.3.1.2 Diarrhea

Prophylactic antidiarrheals will not be used in this protocol. However, diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment.

7.3.1.3 Erythematous Rash with or without Pruritus

As with bortezomib, rash with or without pruritus has been reported with MLN9708 (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 MLN9708 (ixazomib) should be modified and re-initiated at a reduced level from where rash was noted.

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. Study medications should be discontinued in the event of severe, potentially life-threatening rash.

7.3.1.4 Thrombocytopenia

Blood counts should be monitored regularly 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. MLN9708 (ixazomib) administration should be modified as noted as per dose modification recommendations when thrombocytopenia occurs. 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.

7.3.1.5 Neutropenia

Blood counts should be monitored regularly 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. MLN9708 (ixazomib) administration should be modified as noted as per dose modification recommendations when neutropenia occurs. Therapy can be reinitiated at a reduced level upon recovery of ANCs.

7.3.1.6 Fluid Deficit

Dehydration should be avoided since MLN9708 (ixazomib) may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported in patients treated with MLN9708 (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.

7.3.1.7 Hypotension

Symptomatic hypotension and orthostatic hypotension with or without syncope have been

reported with MLN9708 (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.

7.3.1.8 Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome, which ultimately resolved, has been reported with MLN9708 (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.

7.3.1.9 Progressive Multifocal Leukoencephalopathy (PML)

PML, which may be fatal, has occurred in less than 1% of oncology patients receiving MLN9708 (ixazomib) in combination with other cancer therapies. It is not known whether MLN9708 (ixazomib) causes PML; however, the possibility that MLN9708 (ixazomib) may have contributed to PML cannot be excluded. In the event of occurrence of PML, MLN9708 (ixazomib) should be discontinued and supportive care provided as needed.

7.3.1.10 Transverse Myelitis

Transverse myelitis has also been reported with MLN9708 (ixazomib). It is not known if MLN9708 (ixazomib) causes transverse myelitis; however, because it happened to a patient receiving MLN9708 (ixazomib), the possibility that MLN9708 (ixazomib) may have contributed to transverse myelitis cannot be excluded.

7.3.2 MLN4924 (Pevonedistat)

7.3.2.1 MLN4924 (Pevonedistat) Dose Adjustment Based on Serum Transaminases and Total Bilirubin

ALT, AST and bilirubin grading will be determined by CTCAE v5.0 in times per ULN, irrespective of baseline levels.

It is anticipated that LFTs (AST, ALT, and occasionally bilirubin) may be elevated for approximately 48 hours following the end of MLN4924 (pevonedistat) infusion on Cycle 1, Day 1. For elevated LFTs of Grade 2 or 3 that occur on or after Cycle 1, Day 3, MLN4924 (pevonedistat) should be held; once the elevated AST or ALT returns to Grade ≤1, and/or elevated bilirubin returns to ≤1.5×ULN or the patient's baseline level, MLN4924 (pevonedistat)

dose may be resumed. For MLN4924 (pevonedistat), a minimum of one full calendar day between any two doses should be maintained, and a maximum of three doses of MLN4924 (pevonedistat) within the cycle must not be exceeded.

For elevated LFTs of Grade 4 that occur on or after Cycle 1 Day 3, the MLN4924 (pevonedistat) dose should be held for the remainder of the cycle; if the elevated AST or ALT returns to Grade ≤1, and/or elevated bilirubin returns to ≤1.5×ULN or the patient's baseline level, then MLN4924 (pevonedistat) may be restarted at the next cycle at a reduced dose. If the toxicity returns to Grade ≤1 or the patient's baseline status, MLN4924 (pevonedistat) may be re-escalated.

7.3.2.2 MLN4924 (Pevonedistat) Dose Adjustment Based on Hypophosphatemia

If hypophosphatemia is Grade ≥3, study drug treatment should not be resumed until the hypophosphatemia is Grade ≤2. Hypophosphatemia should be evaluated (including severity and etiology), monitored, and treated according to institutional guidelines.

7.3.2.3 MLN4924 (Pevonedistat) Dose Adjustment for Other Toxicities

For other Grade ≥2 nonhematologic toxicities potentially related to MLN4924 (pevonedistat), the MLN4924 (pevonedistat) dose may be reduced at the discretion of the sponsor investigator as clinically indicated. If the toxicity returns to Grade ≤1 or the patient's baseline status, MLN4924 (pevonedistat) may be re-escalated at the next cycle.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agents

8.1.1 MLN9708 (Ixazomib citrate) (NSC 767907)

Chemical Name: 1,3,2-Dioxaborolane-4,4-diacetic acid, 2-[(1*R*)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]-5-oxo

Classification: Proteasome inhibitor

Other Names: Ixazomib ML0070120, MLN2238 citrate ester, Ninlaro®

CAS Registry Number: 1239908-20-3

Molecular Formula: $C_{20}H_{23}BCl_2N_2O_9$ **M.W.**: 517.12 g/mol (ixazomib citrate)

Description: In its solid state**,** MLN9708 is a white to off-white powder. Under physiologic conditions, ixazomib citrate rapidly hydrolyzes to the biologically active form, ixazomib, the boronic acid form of ixazomib citrate.

Mode of Action: MLN9708 is a reversible proteasome inhibitor. MLN9708 preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome. It induced apoptosis of multiple myeloma cell lines *in vitro*.

How Supplied: Takeda supplies and Pharmaceutical Management Branch (PMB), CTEP, Division of Cancer Treatment and Diagnosis (DCTD) distributes MLN9708 as 3 mg and 4 mg capsule strengths (**expressed as boronic acid equivalent**). The capsule strengths are unique colors and packaged as 3 capsules per blister pack.

The hard-capsule formulation consists of ixazomib citrate and the following excipients: microcrystalline cellulose, talc, and magnesium stearate.

Storage: Do not store MLN9708 above 30ºC (or not above 86ºF). Do not freeze.

If a storage temperature excursion is identified, promptly return MLN9708 to not above 30ºC (or not above 86ºF) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Stability studies are ongoing.

Route(s) of Administration: PO

Method of Administration: Take capsule(s) on an empty stomach, 1 hour before or 2 hours after food. Swallow whole capsules with water. Do not open or break capsules.

Missed or delayed dose can be taken only if the next scheduled dose is ≥72 hours away. A missed dose should not be taken within 72 hours of the next scheduled dose. If vomiting occurs after taking a dose, the patient should not repeat the dose. Resume dosing at the time of the next scheduled dose.

Potential Drug Interactions: MLN9708 is metabolized by CYP3A4 (42.3%), 1A2 (26.1%), 2B6 (16%), 2C8 (6%), 2D6 (4.8%), 2C19 (4.8%), and 2C9 (<1%). Co-administration of MLN9708 with clarithromycin did not result in a clinically significant change in the systemic exposure of MLN9708. Co-administration of MLN9708 with rifampin decreased MLN9708 C_{max} by 54% and AUC by 74%. Therefore, avoid concomitant administration of MLN9708 with strong CYP3A4 inducers (such as rifampin, phenytoin, carbamazepine, and St. John's Wort).

MLN9708 is neither a time-dependent nor a reversible inhibitor of CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6, or 3A4/5. MLN9708 (ixazomib) did not induce CYP1A2, CYP2B6, and CYP3A4/5 activity or corresponding immunoreactive protein levels. MLN9708 is not expected to produce drug-drug interactions via CYP inhibition or induction.

MLN9708 is a low affinity substrate of P-gp. MLN9708 is not a substrate of BCRP, MRP2, or hepatic OATPs. MLN9708 (ixazomib) is not an inhibitor of P-gp, BCRP, MRP2, OATP1B1, OATP1B3, OCT2, OAT1, OAT3, MATE1, or MATE2-K. Hence, MLN9708 is not expected to cause transporter-mediated drug-drug interactions.

Patient Implications: There are no human data available regarding the potential effect of MLN9708 on pregnancy or development of the embryo or fetus. Based on clinical data, MLN9708 caused embryo-fetal toxicity in pregnant rats and rabbits at doses resulting in exposures that were slightly higher than those observed in patients receiving the recommended dose. Women should avoid becoming pregnant while being treated with MLN9708. Male and female patients of childbearing potential must use effective contraceptive measures during and for 90 days following treatment.

It is not known whether MLN9708 or its metabolites are present in human milk. Many drugs are present in human milk and as a result, there could be a potential for adverse events in nursing infants. Women should discontinue nursing while receiving MLN9708.

Availability

MLN9708 (ixazomib)is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

MLN9708 (ixazomib)is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.2 MLN4924 (Pevonedistat HCl) (NSC 793435)

Chemical Name: ((1S,2S,4R)-4-{(1S)-2,3-dihydro-1H-inden-1-ylamino]-7H-pyrrolo[2,3-d] pyrimidin-7-yl}-2-hydroxycyclopentyl) methyl sulfamate hydrochloride

Classification: NEDD8-activating enzyme (NAE) inhibitor

Other Names: Pevonedistat, TAK924/MLN4924; MLN4924-003 (hydrochloride salt); MLN4924-001 (free base); ML00644807; ML644507

CAS Registry Number: 905579-51-3 (free base); 1160295-21-5 (hydrochloride salt)

Molecular Formula: $C_{21}H_{26}ClN_5O_4S$

M.W.: 443.52 (free base); 479.98 (hydrochloride salt)

Mode of Action: MLN4924 is an inhibitor of neural precursor cell expressed development down-regulated 8 (NEDD8)-activating enzyme or NAE. NAE is essential in the NEDD8-conjugation pathway to control the activity of a subset of multiprotein complexes that transfer NEDD8 molecules to protein substrates by E3 ligases. NAE inhibitors stop the degradations of a subset of proteins that regulated by the proteasomes.

Description: White to off-white solid with an assay value of 96.0% to 103.0% (w/w) on an anhydrous basis. Acid dissociation constants of $pK_{a1} = 5.16$ and $pK_{a2} = 8.81$.

How Supplied: Takeda supplies and PMB distributes MLN4924 (Pevonedistat HCl) formulated as 10 mg/mL Concentrate for Solution for Infusion. Each single-use vial contains either 50 mg (5 mL) or 44 mg (4.4 mL) free base equivalent [redacted]. The sterile solution is packaged in USP Type I glass vials with rubber stoppers (latex free), aluminum seals with plastic caps.

The current supply is 50 mg (5 mL) with 0.3 mL overfill volume. At a future date, the 44 mg (4.4 mL) vial configuration will replace the 50 mg (5 mL) vial configuration. The 44 mg (4.4 mL) vial contains 0.3 mL overfill volume.

Preparation:
Before use, bring MLN4924 (Pevonedistat HCl) vials to ambient room temperature (15º – 30º C / 59º – 86º F) for 15 minutes. Do not use a water bath to warm up the vials. Return vials to 2º – 8º C (36º – 46º F) storage if not used within 6 hours.

- Use a 250 mL **prefilled** 5% Dextrose (D5W) or 0.9% Normal Saline (NS) IV bag:
    - Remove excess volume from 250 mL D5W or NS prefilled IV bag
    - Add the calculated dose (mL) of pevonedistat
    - Final volume (250 mL) = drug + D5W or NS

- Do not shake; gently mix the IV solution by inverting the IV bag several times
- Inspect the IV solution to ensure it is clear and free of visible particles

- Alternatively, a 250 mL **empty IV bag can be used**:
  - Add the required volume of D5W or NS into the empty IV bag
  - Add the calculated dose (mL) of pevonedistat
  - Final volume (250 mL) = Drug + D5W or NS
  - Do not shake; gently mix the IV solution by inverting the IV bag several times
  - Inspect the IV solution to ensure it is clear and free of visible particles

Materials: PVC or Polyolefin bags; non-DEHP IV bag is preferred but not required.

Storage:
Store MLN4924 (Pevonedistat HCl) refrigerated at 2º – 8º C (36º – 46º F) in its original carton to protect from light.

If a storage temperature excursion is identified, promptly return MLN4924 (Pevonedistat HCl) to 2º – 8º C (36º – 46º F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability:
Stability studies of the intact vials are ongoing.

- Once MLN4924 (Pevonedistat) prepared IV solution is complete, the prepared IV solution must be used within 6 hours when stored at ambient room temperature. Discard the IV bag if it cannot be used within 6 hours.
- Alternatively, the prepared IV solution is stable up to 18 hours when stored at 2º - 8º C (36º – 46º F), after which the IV bag can be used within 3 hours upon removal from 2º - 8º C storage. The prepared IV solution must be brought up to ambient room temperature before administering to patient. If cannot used within 3 hours, the prepared IV solution must be discarded.

Route of Administration: Intravenous

Method of Administration: Infuse over 60 minutes (±10 minutes) through peripheral IV-line, midline or central venous access. The IV infusion can be slowed or stopped and restarted for any associated infusion-related reactions. The total time from the IV preparation to end of IV infusion must not exceed 6 hours. Infusion line can be flushed with 5% Dextrose in Water or 0.9% Normal Saline immediately after IV administration is complete. Protecting IV bag from light during IV infusion is not required.

Potential Drug Interactions: *In vitro*, MLN4924 is metabolized mainly by hepatic CYP3A4/5 and to some extent by CYP2D6 (3%). CYP1A1 and 2J2 appear to be involved in extrahepatic metabolism, which may explain the lack of drug-drug interaction with CY3A4/5 inhibitors. This was demonstrated in an *in vivo* PK study where a moderate

CYP3A inhibitor (*e.g.*, fluconazole) and a strong CYP3A4 inhibitor (*e.g.*, itraconazole, which is also a strong P-gp inhibitor) did not result in interactions when administered with MLN4924. Therefore, drugs that are CYP3A/P-gp inhibitors can be used in patients receiving MLN4924. **Use of strong CYP3A inducers (*e.g.*, rifampin, phenytoin, St. John's wort) with MLN4924 is prohibited**.

In vitro, MLN4924 is **not** an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC_{50} >100 mcM and Ki >50 mcM) but is a weak inhibitor of CYP2B6 and 2C8 (IC_{50} = 97.6 and 23.1 mcM, respectively). MLN4924 causes concentration-dependent decreases in CYP1A2, 2B6, and 3A4/5 mRNA expression and/or activities but is not expected to affect the PK of CYP1A2, 2B6 or 3A4/5 substrates.

MLN4924 is a substrate of P-gp and BCRP, and a weak inhibitor of P-gp, OATP, and BCRP-mediated transport. MLN4924 is unlikely to affect the PK of known P-gp, BCRP, or OATP substrates. Co-administration of BCRP inhibitors (*e.g.*, cyclosporine) is not allowed; consult the protocol document if no suitable alternative exists for the patient.

Because the metabolic and excretion pathways of MLN4924 remain to be fully characterized in humans, the risk of drug-drug interactions between MLN4924 and concomitantly administered drugs are currently informed by available nonclinical and clinical data. As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored.

Availability

MLN4924 (pevonedistat) is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. MLN4924 (pevonedistat) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.4).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Confirmation of patient enrollment onto study is required for initial supply. Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account

status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

8.1.3.2 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

8.1.4 Investigator Brochure Availability

The current versions of the Investigator's Brochures for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about Investigator's Brochures access may be directed to the PMB Investigator's Brochures Coordinator via email.

8.1.5 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
- Investigator's Brochures Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a multicenter phase 1b, open-label study to assess the safety and tolerability of MLN4924 (pevonedistat) and MLN9708 (ixazomib) in patients with RRMM, and to determine the MTD/tentative RP2D of the combination.

Primary Endpoints:

- Safety of MLN4924 (pevonedistat) and MLN9708 (ixazomib) given in combination
- Determine the MTD of the combination

Secondary Endpoints:

- PK characterization of MLN4924 (pevonedistat) in combination with MLN9708 (ixazomib)
- Information on correlative pharmacodynamic measures (NRF2 target genes) in both PI-sensitive and PI-refractory patients

All patients who receive any amount of the study drug will be evaluable for toxicity. The DLT-evaluable period will be during Cycle 1, although toxicity will be monitored throughout the course of treatment. The primary analysis will occur after all patients have either discontinued the study or completed at least 6 months of treatment.

Descriptive statistics will be provided for selected demographic, safety, PK, and pharmacodynamic data by dose and time as appropriate. Descriptive statistics on continuous data will include means, medians, standard deviations, and ranges, while categorical data will be summarized using frequency counts and percentages. Graphical summaries of the data may be presented.

Efficacy analysis will be performed for all patients in the dose escalation and dose expansion part (MTD of the combination in PI-sensitive and PI-refractory patients) of the study. Parameters assessed will include stringent complete response (sCR), CR, VGPR, PR, and SD per IMWG Uniform Response criteria and minor response (MR) per European Group for Blood and Marrow Transplantation (EBMT) criteria. In addition, overall response rate (defined as greater than or equal to PR across all cycles of treatment), response duration, time-to-response (TTR), PFS, and OS will be assessed.

Best overall response categories will be tabulated by dose cohort and overall for the IMWG categories of sCR, CR, VGPR, PR, SD, PD, and relapse and the EBMT category of MR. A two-sided 95% exact binominal confidence intervals (CI) will be calculated for each category. The myeloma response rate (responses ≥PR) will also be tabulated by dose cohort and overall. The myeloma response rate and each of the best overall response categories will be compared between dose cohorts with Chi-square test. Survival analyses will be done using Kaplan-Meier method, log-rank test, and Cox model. The endpoints of time to event analyses will include TTR, duration of response, PFS, and OS, as data allow. If there is not enough data for survival analyses, the data will be summarized by descriptive statistics.

9.2 Sample Size/Accrual Rate

The dose escalation part of this study consists of 7 dose levels including at least 3 and up to 6 patients for a minimum of 18 patients if no DLT is reached, or a maximum of 42 patients. An exploratory expansion phase including 24 patients at the RP2D is also planned for a total of 42-66 patients in total. Based on prior phase 1 and 2 studies at Emory targeting a similar patient population, we estimate 2 patients will be accrued every month, suggesting that 21-33 months will be needed to meet the total sample size. Please note this assumes no interruption in accrual.

For the expansion cohort, 24 patients will be enrolled, 12 each with PI-sensitive and PI-refractory disease. In the PI-sensitive group, success will be defined as >6 patients having a PR or better at the RP2D. In the PI refractory population, >2 patients with PR or better will define success.

For a maximum of 66 patients, we would estimate 50% male and 50% female. Per institutional experience, we would expect ~30% African Americans and ~5% Hispanic or Latino.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
Black or African American	9	9	1	1	**20**
White	22	22	1	1	**46**
Total	**31**	**31**	**2**	**2**	**66**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

9.3 Analysis of Secondary Endpoints

A full PK profile of MLN4924 (pevonedistat) will be examined to assess exposure-response relationships with various pharmacodynamic endpoints (*i.e.*, changes, toxicity, and efficacy). MLN4924 (pevonedistat) concentrations in these samples will be quantitatively measured using a liquid chromatography/tandem mass spectrometry (LC/MS/MS) method in place at Covance under contract with Takeda. For MLN4924 (pevonedistat), the individual PK parameters from a single dose will be estimated for C_{max}, AUC, $t_{1/2}$, apparent CL/F, and apparent volume of distribution (V/F) using non-compartmental or compartmental PK methods with the software WinNonlin. Advanced population PK methods may be employed to assess the link between drug exposure and biological effects and efficacy. The PK variables and changes in pharmacodynamic markers will be tabulated and descriptive statistics (*e.g.*, geometric means and

CV) calculated for each dose level. A more limited PK analysis will be performed for MLN9708 (ixazomib) to assess accumulation, with blood samples (3 mL) to be taken predose (within 1 hour) and 1 hour ±10 min postdose on Days 1 and 15 of Cycles 1 and 3. Plasma MLN9708 (ixazomib) concentrations will be measured using a validated LC/MS/MS method.

PK parameters (*i.e.*, $t_{1/2}$, CL, and AUC) changes will be compared across dose levels using the parametric General Linear Model (GLM) or nonparametric Kruskal-Wallis test, depending on the distribution of data. Exploratory correlative studies with pharmacodynamic (biological endpoints, toxicity, and efficacy) will be analyzed using Pearson or Spearman's correlation coefficient and tested with Wald's test. Significance for comparisons will be at the $P<0.05$ level.

For the biomarker study of *NQO1* and *SLC7A11*, descriptive statistics will first be used to summarize their gene expression in whole blood by RT-PCR. Biomarker data will also be displayed graphically, where appropriate. Depending on whether data is normally distributed, Person or Spearman's correlation coefficient will be used to measure the correlations of *NQO1* and *SLC7A11* with the dosage of MLN4924 (pevonedistat), and then tested with Wald's test. GLM will be used to compare each of the biomarkers (*NQO1* and *SLC7A11*) between different dose levels of MLN4924 (pevonedistat) with and without adjusting for other factors. Logistics regression model will be further employed to test the adjusted effect of each biomarkers (*NQO1* and *SLC7A11*) on the response rate after adjusting for dosage of MLN4924 (pevonedistat) as well as other factors.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

AE monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks List(s) (CAEPRs)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential AE associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification.

NOTE: Report AEs on the SPEER ONLY IF they exceed the Grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the Grades to determine if expedited reporting is required.

10.1.1 CAEPRs for CTEP IND Agents

10.1.1.1 CAEPR for MLN9708 (ixazomib)

Frequency is provided based on 1122 patients. Below is the CAEPR for MLN9708 (Ixazomib citrate).

Version 2.1, March 26, 2022[1]

Adverse Events with Possible Relationship to MLN9708 (Ixazomib citrate) (CTCAE 5.0 Term) [n= 1122]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
		Thrombotic thrombocytopenic purpura	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		
Diarrhea			***Diarrhea (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***

Adverse Events with Possible Relationship to MLN9708 (Ixazomib citrate) (CTCAE 5.0 Term) [n= 1122]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
		Edema limbs	
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (hepatotoxicity)[2]	
INFECTIONS AND INFESTATIONS			
	Upper respiratory infection		***Upper respiratory infection (Gr 2)***
INVESTIGATIONS			
	Neutrophil count decreased		***Neutrophil count decreased (Gr 2)***
	Platelet count decreased		***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
NERVOUS SYSTEM DISORDERS			
	Headache		
	Nervous system disorders - Other (peripheral neuropathies NEC, peripheral neuropathy, peripheral motor neuropathy)		***Nervous system disorders - Other (peripheral neuropathies NEC, peripheral neuropathy, peripheral motor neuropathy) (Gr 2)***
	Peripheral sensory neuropathy		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity have each been reported in <1% of patients treated with MLN9708. Events of liver impairment have been reported. Monitor hepatic enzymes regularly and adjust dosing for Grade 3 or 4 symptoms.

Adverse events reported on MLN9708 (Ixazomib citrate) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MLN9708 (Ixazomib citrate) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Myocardial infarction
EYE DISORDERS - Blurred vision; Retinal detachment
GASTROINTESTINAL DISORDERS - Enterocolitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Disease progression; Flu like symptoms; Malaise
HEPATOBILIARY DISORDERS - Bile duct stenosis
INFECTIONS AND INFESTATIONS - Bronchial infection; Fungemia; Infections and infestations - Other (Parainfluenza Infection); Lung infection; Pharyngitis; Sepsis; Shingles; Sinusitis
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall; Injury, poisoning and procedural complications - Other (femoral neck fracture); Spinal fracture
INVESTIGATIONS - Aspartate aminotransferase increased; Lymphocyte count decreased; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hypokalemia; Hyponatremia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle weakness lower limb; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (non-Hodgkin's lymphoma); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (plasma cell myeloma); Tumor pain
NERVOUS SYSTEM DISORDERS - Dizziness; Dysgeusia
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchial obstruction
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Erythema multiforme; Pruritus
VASCULAR DISORDERS - Hypotension

Note: MLN9708 (Ixazomib citrate) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.1.1.2 CAEPR for MLN4924 (Pevonedistat)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 474 patients.* Below is the CAEPR for MLN4924 (Pevonedistat HCl).

> **NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, July 10, 2020[1]

Adverse Events with Possible Relationship to MLN4924 (Pevonedistat HCl) (CTCAE 5.0 Term) [n= 474]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
CARDIAC DISORDERS			
		Sinus tachycardia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
	Pain		***Pain (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Lung infection		***Lung infection (Gr 2)***
	Upper respiratory infection		
	Urinary tract infection		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		***Bruising (Gr 2)***
INVESTIGATIONS			
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
	GGT increased		
	Platelet count decreased		***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
	Hypercalcemia		
	Hyperglycemia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		

Adverse Events with Possible Relationship to MLN4924 (Pevonedistat HCl) (CTCAE 5.0 Term) [n= 474]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		***Muscle cramp (Gr 2)***
Myalgia			***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
	Nervous system disorders - Other (neuropathy peripheral, peripheral neuropathy)		
	Paresthesia		
PSYCHIATRIC DISORDERS			
	Anxiety		
	Confusion		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		
	Hypoxia		
	Pleural effusion		
	Productive cough		
	Respiratory, thoracic and mediastinal disorders - Other (rales)		
	Wheezing		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		
	Purpura		
VASCULAR DISORDERS			
	Hypotension		***Hypotension (Gr 2)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Adverse events reported on MLN4924 (Pevonedistat HCl) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MLN4924 (Pevonedistat HCl) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other

(pancytopenia); Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocarditis
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Ascites; Dyspepsia; Gastrointestinal disorders - Other (gastrointestinal necrosis); Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Ileus; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Generalized edema; Multi-organ failure; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Bacteremia; Sepsis; Sinusitis; Skin infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall
INVESTIGATIONS - Investigations - Other (brain natriuretic peptide increased); Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hyperuricemia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Spinal cord compression
PSYCHIATRIC DISORDERS - Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Dysuria; Renal and urinary disorders - Other (renal impairment); Urinary retention
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Nasal congestion; Oropharyngeal pain; Respiratory failure; Rhinorrhea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular
VASCULAR DISORDERS - Hypertension; Phlebitis; Thromboembolic event

Note: MLN4924 (Pevonedistat HCl) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

10.2 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 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the Grade is above the Grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 RAVE-CTEP-AERS Integration

The Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline AEs entered in Rave to determine whether they require expedited reporting, and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

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

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders and administration site conditions." 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.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted electronically within 10 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 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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

Effective Date: May 5, 2011

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions**.

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 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.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. 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.

10.7 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 AE reporting unless otherwise specified.

11. STUDY CALENDAR

Schedules shown in the Study Calendar below are provided as an example and should be modified as appropriate.

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	Cycle 1				Cycle 2				Cycle 3				Cycle 4+				Off Study[a]
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5*	Wk 6	Wk 7	Wk 8	Wk 9*	Wk 10	Wk 11	Wk 12	Wk 13*	Wk 14	Wk 15	Wk 16	
MLN9708 (ixazomib)		A	A	A		A	A	A		A	A	A		A	A	A		
MLN4924 (Pevonedistat)		B	B	B		B	B	B		B	B	B		B	B	B		
Informed consent	X																	
Demographics	X																	
Medical history	X																	
Concurrent meds	X	X----------X																
Physical exam	X	X				X				X				X				X
Vital signs[h, i]	X	X	X			X	X			X	X			X	X			X
Height	X																	
Weight	X	X				X				X				X				X
Performance status	X	X				X				X				X				X
CBC w/diff, platelets	X	X	X	X		X	X	X		X	X	X		X	X	X		X
Chemistry Panel[b]	X	X	X	X		X	X	X		X	X	X		X	X	X		X
EKG	X																	X
Echocardiogram	X																	
Adverse event evaluation		X----------X																X
Serum B-HCG	X	X				X				X				X				
Urinalysis and coagulation (including PT and aPTT)	X																	
Plasma collection for MLN4924 (pevonedistat) and MLN9708 (ixazomib) PK[j]		X[c]		X[d]						X[d]		X[d]						
Blood collection for NRF2 target gene studies	X	X[e]																
Myeloma laboratory testing assessments[f]	X					X				X				X				X
Extramedullary disease assessment[g]	X					X[f]				X[f]				X[f]				X[f]

	Pre-Study	Cycle 1				Cycle 2				Cycle 3				Cycle 4+				Off Study[a]
		Wk 1	Wk 2	Wk 3	Wk 4	Wk 5*	Wk 6	Wk 7	Wk 8	Wk 9*	Wk 10	Wk 11	Wk 12	Wk 13*	Wk 14	Wk 15	Wk 16	
Skeletal survey/CT scan	X	Repeated during treatment if clinically indicated to confirm response or PD																
Bone marrow aspirate[k]	X																	

*Assessments are treatments on D1 of each subsequent cycle after C1 can be done in a ±2 day window

A: MLN9708 (ixazomib): Dose as assigned on Days 1, 8, and 15 of each 28-day cycle.

B: MLN4924 (pevonedistat): Dose as assigned on Days 1, 8, and 15 of each 28-day cycle.

a: Off-study evaluation.

b: Chemistry panel will include the following: BUN, creatinine, sodium, potassium, chloride, carbon dioxide, glucose, bilirubin, alkaline phosphatase (ALP), LDH, AST, ALT, total protein, albumin, magnesium, phosphate, urate, direct bilirubin, and calcium. ALP, ALT, AST, and total bilirubin assessments must be performed and read prior to dosing MLN4924 (pevonedistat).

c: Plasma for MLN4924 (pevonedistat) and MLN9708 (ixazomib) PK profiles. Time points to be collected for PK profiles are: pre-dose and 1 hr ±10 min after initiation of infusion. Additional time points to be collected for MLN4924 (pevonedistat) PK profile are: 0.5 hr ±10 min, 2 hr ±10 min, 2.5 hr ±10 min, 5 hrs ±30 min, 8 hr ±45 min, and 21 hrs ±2 hrs after initiation of infusion.

d: Plasma for MLN9708 (ixazomib) PK profile. Time points to be collected are: pre-dose and 1 hr ±10 min after initiation of infusion.

e: To be collected 4 hours after completion of pevonedistat infusion on Cycle 1, Day 1.

f: M-protein quantification by SPEP and UPEP, Serum Free Light Chain Assay, 24-hour urine collection, and immunofixation of serum and urine are to be performed at baseline within 7 days prior to study, prior to each cycle thereafter and at time of study discontinuation (if last tests were >4 weeks). Repeat MM labs on Day 1 of Cycle 1 if screening done >7 days prior to study entry.

g: Only when clinically indicated or with known history, prior to study (28 days) and every cycle (with known history) or upon clinical suspicion of progressive disease. This may include physical exam with measurements, CT scan of the chest, abdomen/pelvis, ultrasound of the liver/spleen or abdomen.

h: Vital signs are to be taken with the patient in the supine or sitting position.

i: To include blood pressure, heart rate, and temperature taken at Screening; Day 1 and Day 8 of each cycle; at off study; and as clinically indicated.

j: PK samples will only be collected during the dose escalation portion.

k; Bone marrow aspirate and biopsy is optional at screening.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated every 4 weeks. In addition to a baseline scan, confirmatory scans will also be obtained 4 weeks following initial documentation of an objective response.

12.1 Antitumor Effect – Hematologic Tumors

Responses will be evaluated utilizing the IMWG Response Criteria as per the table below.

Response	***IMWG criteria***
Stringent Complete Response (sCR)	CR as defined below plus: • Normal free light chain (FLC) ratio, and • absence of clonal cells in bone marrow by immunohistochemistry or 2–4 color flow cytometry.
Complete Response (CR)	• Negative immunofixation on the serum and urine, • disappearance of any soft tissue plasmacytomas, and • <5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
Very Good Partial Response (VGPR)	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or • ≥90% reduction in serum M-protein plus urine M-protein level <100 mg/24 hours. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
Partial Response (PR)	• 50% reduction of serum M-protein and reduction in 24 hour urinary M-protein by ≥90% or to <200 mg/24 hours. • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.

	• If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30%. • In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required.
Stable Disease (SD)	• Not meeting criteria for CR, VGPR, PR or progressive disease
Minimal Response (MR)	• 25% but < 49% reduction of serum M protein *and* reduction in 24 hour urine M-protein by 50 to 89% which still exceeds 200 mg/24 hours. • In addition to the above criteria, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required. • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).
Progressive disease	Increase of ≥25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥0.5 g/dL), and/or • Urine M-component (the absolute increase must be ≥200 mg/24 hours), and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL. • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥10%). • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas. • Development of hypercalcemia (corrected serum calcium >11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder.

Adapted from Durie *et al*. (2006). All response categories (CR, sCR, VGPR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was

measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥1 gm/dL are sufficient to define response if starting M-component is ≥5g/dL.

IMWG clarification for coding PD: Clarified that Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

14. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

AE lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

14.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the Phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

14.2 Data Reporting

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account, and
- Assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.
    - To hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,

- To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

Upon initial site registration approval for the study in Regulatory Support System (RSS), all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

14.2.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted three times annually (one annual site visit and two data audits). For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

- Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the Principal Investigator(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will

be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the Investigational Drug Branch (IDB), CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the Principal Investigator and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any DLTs. CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The Principal Investigator is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

14.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified

queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization (LPO) for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

14.4 CTEP Multicenter Guidelines

N/A

14.5 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to

restrict NCI's participation in the proposed combination protocol.

b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human patients, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or Principal Investigator for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

15. REFERENCES

Bauer T.M., D.R.H., C.B. Lee, *et al*. (2016). Investigational NEDD8-activating enzyme inhibitor pevonedistat plus chemotherapy in patients with solid tumors (phase 1b study): Activity of pevonedistat plus carboplatin/paclitaxel. *J Clin Oncol*. 34:2580.

Bhatia, S., A.C. Pavlick, P. Boasberg*, et al.* (2016). A phase I study of the investigational NEDD8-activating enzyme inhibitor pevonedistat (TAK-924/MLN4924) in patients with metastatic melanoma. *Invest New Drugs*. 34:439-449.

Chauhan, D., Z. Tian, B. Zhou*, et al.* (2011). In vitro and in vivo selective antitumor activity of a novel orally bioavailable proteasome inhibitor MLN9708 against multiple myeloma cells. *Clin Cancer Res*. 17:5311-5321.

Dalton, W.S. (2004). The proteasome. *Semin Oncol*. 31:3-9; discussion 33.

Dimopoulos, M.A., J. Laubach, M.A. Echeveste Gutierrez, *et al*. (2017). Efficacy and safety of long-term ixazomib maintenance therapy in patients (pts) with newly diagnosed multiple myeloma (NDMM) not undergoing transplant: An integrated analysis of four phase 1/2 studies. *Blood*. 130:A902.

Durie, B.G., J.L. Harousseau, J.S. Miguel, *et al*. (2006). International uniform response criteria for multiple myeloma. *Leukemia*. 20:1467-1473.

Garcia-Gomez, A., D. Quwaider, M. Canavese*, et al.* (2014). Preclinical activity of the oral proteasome inhibitor MLN9708 in Myeloma bone disease. *Clin Cancer Res*. 20:1542-1554.

Gu, Y., J.L. Kaufman, L. Bernal*, et al.* (2014). MLN4924, an NAE inhibitor, suppresses AKT and mTOR signaling via upregulation of REDD1 in human myeloma cells. *Blood*. 123:3269-3276.

Gupta, N., M.J. Hanley, K. Venkatakrishnan, *et al*. (2015). Abstract B147: A phase 1 drug-drug interaction study between ixazomib, an oral proteasome inhibitor, and rifampin in patients (pts) with advanced solid tumors. *Mol Cancer Ther*. 14:Abstract B147:

Hou, J., J. Jin, Y. Xu, *et al*. (2017). Improved PFS and OS with ixazomib plus lenalidomide-dexamethasone (IRd) vs plascebo-Rd in patients (pts) with relapsed/refractory multiple myeloma (RRMM): Final data from the phase 3 china continuation of TOURMALINE-MM1. *Clin Lymphoma Myeloma Leuk*. 17:e67.

Ixazomib Investigator's Brochure. (2017). Millennium Pharmaceuticals, Inc. Edition 11, July 27, 2017.

Kumar, S.K., M.A. Dimopoulos, E. Kastritis*, et al.* (2017). Natural history of relapsed myeloma, refractory to immunomodulatory drugs and proteasome inhibitors: a multicenter IMWG study. *Leukemia*. 31:2443-2448.

Kupperman, E., E.C. Lee, Y. Cao*, et al.* (2010). Evaluation of the proteasome inhibitor MLN9708 in preclinical models of human cancer. *Cancer Res*. 70:1970-1980.

Lin, J.J., M.A. Milhollen, P.G. Smith*, et al.* (2010). NEDD8 targeting drug MLN4924 elicits DNA re-replication by stabilizing Cdt1 in S Phase, triggering checkpoint activation, apoptosis and senescence in cancer cells. *Cancer research*. 70:10310-10320.

Lockhart C.A., T.M.B., D. Harvey, *et al*. (2015). Phase 1b trial of investigational NEDD8-activating enzyme (NAE) inhibitor pevonedistat (TAK-924/MLN4924) in combination with docetaxel, paclitaxel/carboplatin, or gemcitabine in patients with solid tumors. *Mol Cancer Ther*. 14:B26.

McMillin, D.W., H.M. Jacobs, J.E. Delmore*, et al.* (2012). Molecular and cellular effects of NEDD8-activating enzyme inhibition in myeloma. *Mol Cancer Ther*. 11:942-951.

Milhollen, M.A., U. Narayanan, T.A. Soucy*, et al.* (2011). Inhibition of NEDD8-activating enzyme induces rereplication and apoptosis in human tumor cells consistent with deregulating CDT1 turnover. *Cancer Res*. 71:3042-3051.

Moreau, P., T. Masszi, N. Grzasko*, et al.* (2016). Oral ixazomib, lenalidomide, and dexamethasone for multiple myeloma. *N Engl J Med*. 374:1621-1634.

Noone, A.M., N. Howlader, M. Krapcho*, et al.* (2018). SEER Cancer Statistics Review, 1975-2015, National Cancer Institute. Bethesda, MD. Based on November 2017 SEER data submission, posted to the SEER web site, April 2018.

Package Insert. (2015). NINLARO® (ixazomib) capsules, for oral use. Millennium Pharmaceuticals, Inc., Cambridge, MA.

Package Insert. (2015). VELCADE (bortezomib) for injection. Millennium Pharmaceuticals, Inc., Cambridge, MA.

Pevonedistat Investigator's Brochure. (2017). Millennium Pharmaceuticals, Inc. Edition 9, August 10, 2017.

Podust, V.N., J.E. Brownell, T.B. Gladysheva*, et al.* (2000). A Nedd8 conjugation pathway is essential for proteolytic targeting of p27(Kip1) by ubiquitination. *PNAS*. 97:4579-4584.

Read, M.A., J.E. Brownell, T.B. Gladysheva*, et al.* (2000). Nedd8 modification of cul-1 activates SCF(beta(TrCP))-dependent ubiquitination of IkappaBalpha. *Mol Cell Biol*. 20:2326-2333.

Richardson, P.G., R. Baz, M. Wang*, et al.* (2014). Phase 1 study of twice-weekly ixazomib, an oral proteasome inhibitor, in relapsed/refractory multiple myeloma patients. *Blood*. 124:1038-1046.

Sarantopoulos, J., G.I. Shapiro, R.B. Cohen, *et al.* (2016). Phase I Study of the Investigational NEDD8-Activating Enzyme Inhibitor Pevonedistat (TAK-924/MLN4924) in Patients with Advanced Solid Tumors. *Clin Cancer Res*. 22:847-857.

Shah, J.J., A.J. Jakubowiak, O.A. O'Connor, *et al.* (2016). Phase I Study of the Novel Investigational NEDD8-Activating Enzyme Inhibitor Pevonedistat (MLN4924) in Patients with Relapsed/Refractory Multiple Myeloma or Lymphoma. *Clin Cancer Res*. 22:34-43.

Soucy, T.A., P.G. Smith, M.A. Milhollen, *et al.* (2009). An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. *Nature*. 458:732.

Swords R.T., M.R.S., M.B. Maris, *et al*. (2014). Pevonedistat (MLN4924), an investigational, first-in-class NAE inhibitor, in combination with azacitidine in elderly patients with acute myeloid leukemia (AML) considered unfit for conventional chemotherapy: Updated results from the phase 1 C15009 trial. *Blood*. 124:2313.

Swords, R.T., H.P. Erba, D.J. DeAngelo, *et al.* (2015). Pevonedistat (MLN4924), a First-in-Class NEDD8-activating enzyme inhibitor, in patients with acute myeloid leukaemia and myelodysplastic syndromes: a phase 1 study. *Br J Haematol*. 169:534-543.

Walker, R.M., E. Koenig, G. Mulligan, *et al*. (2011) Development, validation, and clinical implementation of a peripheral blood RT-PCR pharmacodynamic assay for MLN4924, an investigational small molecule inhibitor of NEDD8-activating enzyme (NAE). Proceedings of the AACR-NCI-EORTC International Conference: Molecular Targets and Cancer Therapeutics; 2011 Nov 12-16; San Francisco, CA. Philadelphia (PA): AACR. *Mol Cancer Ther*. 10(11 Suppl):A196.

APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B PATIENT CLINICAL TRIAL WALLET CARD – MLN9708 (IXAZOMIB)

NIH NATIONAL CANCER INSTITUTE

CLINICAL TRIAL WALLET CARD

Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.

Patient Name:
Diagnosis:
Study Doctor:
Study Doctor Phone #:
NCI Trial #: 10249
Study Drug(S): **MLN9708 (Ixazomib)**

Version FEB/2019

For more information: 1-800-4-CANCER

cancer.gov | clinicaltrials.gov

APPENDIX C PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD – MLN4924 (PEVONEDISTAT)

Information for Patients, Their Caregivers and Non-Study Healthcare Team on Possible Interactions with Other Drugs and Herbal Supplements

Patient Name:	**Diagnosis:**	**Trial #:**	10249
Study Doctor:	**Study Doctor Phone #:**	**Study Drug(s):**	MLN4924 (Pevonedistat)

Please show this paper to all your healthcare providers (doctors, physician assistants, nurse practitioners, pharmacists), and tell them you are taking part in a clinical trial sponsored by the National Cancer Institute.

These are the things that your healthcare providers need to know:
MLN4924 (pevonedistat) interacts with certain specific enzyme in your liver or other tissue like the gut and certain transport proteins that help move drugs in and out of cell.

	Explanation
CYP isoenzymes	The enzymes in question are CYP3A4/5. MLN4924 (pevonedistat) is broken down by CYP3A4/5 and may be affected by drugs that are moderate or strong inducers of CYP3A4/5. Use of CYP3A4 inducers (*e.g.*, St. Jon's Wort, rifampin, phenytoin) is not allowed while taking MLN4924.
Transport proteins	The transporter enzymes and proteins in question are P-glycoprotein (P-gp), OATP and BCRP. MLN4924 is moved in and out of cells/organs by P-gp and BCRP. Use caution with concomitant drugs that are inhibitors of P-gp. Concurrent use of drugs that are BCRP inhibitors (*e.g.*, cyclosporine) is not allowed. MLN4924 may affect the ability of other drugs to be moved in and out of cells by inhibiting P-gp, OATP and BCRP. Use substrates of these transport proteins with caution.

These are the things that you need to know:
The study drug MLN4924 (pevonedistat), may interact with other drugs which can cause side effects. For this reason, it is very important to tell your doctors about all your medicines, including: (a) medicines you are taking before this clinical trial, (b) medicines you start or stop taking during this study, (c) medicines you buy without a prescription (over-the-counter remedy), (d) herbals or supplements (*e.g.* St. John's Wort). It is helpful to bring your medication bottles or an updated medication list with you.

Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered moderate or strong inhibitors or inducers of CYP3A4/5, P-gp, OATP and BCRP.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects. Avoid ingesting grapefruit and grapefruit juice.
- Make sure your doctor knows to avoid certain prescription medications.
- Your regular health care provider should check a frequently updated medical reference or call your study doctor before prescribing any new medicine or discontinuing any medicine.

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE **DRUG INTERACTIONS**
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** MLN4924 (pevonedistat) interacts with enzymes in your liver or other tissue like the gut, transport proteins that help move drugs in and out of cells and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** 10249 **Study Drug(S):** MLN4924 (pevonedistat)	**Use caution and avoid the following drugs if possible:** St. John's Wort, grapefruit or grapefruit juice	Your healthcare providers should be aware of any medicines that are strong inhibitors/inducers of CYP3A4/5, P-gp and OATP. Drugs that are CYP3A4/5 inducers (e.g., rifampin, St. John's Wort), or BCRP inhibitors (e.g., cyclosporine) ae not allowed. **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.	Version JAN/2019
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

APPENDIX D NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.