Pevonedistat as a Single Agent and in Combination with Chemotherapy in Patients with Malignant Mesothelioma

PROTOCOL FACE PAGE FOR MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

OneMSK Sites	
Manhattan	All Protocol Activities
Basking Ridge	All Protocol Activities
Rockville Centre	All Protocol Activities
Westchester	All Protocol Activities
Commack	All Protocol Activities
Monmouth	All Protocol Activities
Bergen	All Protocol Activities
Nassau	All Protocol Activities

Participating Institutions – If multicenter study coordinated by MSK:	**PI's Name**	**Site's Role**
MD Anderson Cancer Center	Filippo Giancotti, MD	Specimen Analysis

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1.1 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title:	Pevonedistat as a Single Agent and in Combination with Chemotherapy in Patients with Malignant Mesothelioma
Study Design:	This study is a single institution trial with two cohorts to test the efficacy of the NEDD8 inhibitor, pevonedistat as a single agent in patients with NF2 mutant MM (Cohort 1), and also to test the safety of pevonedistat in combination with standard chemotherapy, pemetrexed/cisplatin (Cohort 2).
Study Objectives:	Primary Objectives Cohort 1: To determine the clinical benefit rate (CR + PR + SD) of single agent pevonedistat at 18 weeks in patients with previously treated MM that has an NF2 mutation Cohort 2: To establish the safety of the combination of pevonedistat and pemetrexed/cisplatin in patients with previously untreated MM, and determine the recommended phase II dose. Secondary Objectives To determine the progression-free and overall survival in both cohorts. To determine the response rate of single agent pevonedistat in previously treated patients with MM, and the response rate of pevonedistat plus pemetrexed/cisplatin in previously untreated patients. To explore downstream mechanistic biomarkers of pevonedistat in on-treatment biopsy samples from patients in cohort 1.
Patient Population:	Patients with unresectable malignant pleural or peritoneal mesothelioma
Number of patients:	Cohort 1: Maximum of 18 patients Cohort 2: Maximum of 24 patients
Inclusion Criteria:	Both cohorts: ○ Patients must have a histologically confirmed diagnosis of epithelioid, sarcomatoid, or mixed-type malignant pleural or peritoneal mesothelioma that is not amenable to surgery. ○ Patients must have measurable disease according to the modified RECIST criteria for pleural mesothelioma, or standard RECIST for peritoneal mesothelioma. ○ Patients must have adequate tissue sample available for molecular profiling with MSK-IMPACT (archived tissue block or 15-20 unstained slides). Patients will sign a separate informed document (IRB #12-245) to allow this to be performed.

- Patients must be at least 18 years of age.
- Karnofsky performance status ≥ 70%.
- Adequate renal function: serum creatinine ≤ 1.5 x ULN.
- Clinical laboratory values within the following parameters (repeat if more than 7 days before the first dose):
  - Albumin > 2.7 g/dL
- Patients must have adequate hepatic function as defined by:
  - AST and ALT ≤ 2.5 x ULN
  - Total bilirubin ≤ upper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤ 1.5 x ULN of the direct bilirubin.
- Patients must have adequate bone marrow function as defined by:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Hemoglobin ≥ 9 g/dL.
- Female patients who
  - Are postmenopausal (see Appendix for definition) for at least 1 year before the screening visit, OR
  - Are surgically sterile, OR
  - If they are of childbearing potential:
    - Agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see Appendix), at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug (female and male condoms should not be used together), or
    - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)
- Male patients, even if surgically sterilized (i.e., status post vasectomy), who:
  - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug (female and male condoms should not be used together), or
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)
- Signed informed consent

	Cohort 1: o Patients must have received at least one and no more than four prior systemic therapy regimens. At least one of the regimens must have included pemetrexed and a platinum. o Patients must have MM that harbors an NF2 mutation as determined by any CLIA lab certified NGS platform. Cohort 2: o Patients must not have previously received treatment with chemotherapy for MM. o Patients must not have ≥ grade 2 peripheral neuropathy. o Patients must not have hearing deficits requiring the use of a hearing aid.
Exclusion Crite ria:	o Patients currently receiving anticancer therapies or who have received anticancer therapies within 3 weeks of the start of study drug including chemotherapy, biologics, targeted therapies, or immunologics. o Treatment with any investigational products within 4 weeks before the first dose of any study drug. o Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures. o Patients currently receiving radiation therapy, or who have received radiation within 2 weeks from the start of therapy. o Patients who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study. o 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 nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone resection. o Life-threatening illness unrelated to cancer. o Patients with uncontrolled coagulopathy or bleeding disorder. o Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as: ▪ Known cardiopulmonary disease defined as: • Unstable angina • Congestive heart failure (New York heart Association Class III or IV) • Myocardial infarction (MI) within 6 months prior to first dose (patients who had ischemic heart disease such as ACS, MI and/or revascularization greater than 6 months

	before screening and who are without cardiac symptoms may enroll). • Cardiomyopathy • Clinical significant arrhythmia o Polymorphic ventricular fibrillation or torsade de pointes. o Permanent atrial fibrillation [a fib], defined as continuous a fib ≥ 6 months. o Persistent a fib, defined as sustained a fib lasting > 7 days and/or requiring cardioversion in the 4 weeks before screening o Grade 3 a fib defined as symptomatic and incompletely controlled medically, or controlledwith device (e.g. pacemaker), or ablation o Patients with paroxysmal a fib or < Gr 3 a fib for period of at least 6 months are permitted to enroll provided that their rate is controlled on a stable regimen. o Implantable cardioverter defibrillator o Moderate to severe aortic and/or mitral stenosis or other valvulopathy (ongoing) o Symptomatic pulmonary hypertension ▪ Active infection requiring IV antibiotic, antiviral, or anti-fungal medications within 2 weeks of starting study drug. ▪ Known history of HIV seropositivity o Known 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. o Known hepatic cirrhosis or severe pre-existing hepatic impairment o Uncontrolled high blood pressure (i.e., systolic blood pressure > 180 mm Hg, diastolic blood pressure > 95 mm Hg). o Prolonged rate corrected QT (QTc) interval ≥500 msec, calculated according to institutional guidelines. o Left ventricular ejection fraction (LVEF) < 50% as assessed by echocardiogram or radionuclide angiography. o Known central nervous system (CNS) involvement. o Female patients who are both lactating and breast feeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

	○ 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). ○ 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). ○ Patients with a currently active second malignancy requiring treatment. ○ Treatment with clinically significant metabolic enzyme inducers within 14 days before the first dose of the study drug. Clinically significant metabolic enzyme inducers are not permitted during this study.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objectives

Cohort 1: To determine the clinical benefit rate (CR + PR + SD) of single agent pevonedistat at 18 weeks in patients with previously treated MM that has an NF2 mutation.

Cohort 2: To establish the safety of the combination of pevonedistat and pemetrexed/cisplatin in patients with previously untreated MM, and determine the recommended phase II dose.

Secondary Objectives

To determine the progression-free and overall survival in both cohorts.

To determine the response rate of single agent pevonedistat in previously treated patients with MM, and the response rate of pevonedistat plus pemetrexed/cisplatin in previously untreated patients.

To determine the PK for pevonedistat in combination with chemotherapy.

To explore downstream mechanistic biomarkers of pevonedistat activity in on treatment biopsy samples from patients in cohort 1. NEDD8-Cullin4 adduct, phosphorylated YAP and TAZ in on-treatment biopsy samples using western blot and qPCR.

3.1 BACKGROUND AND RATIONALE

Malignant Mesothelioma (MM)

MM is an uncommon tumor afflicting up to 3,000 patients annually in the United States. While MM primarily spreads locally within the pleura, the majority of patients present with disease invading the chest wall or mediastinum and therefore not amenable to surgery. For those patients, palliative chemotherapy is the only treatment option. The standard first-line chemotherapy regimen for both pleural and peritoneal disease, pemetrexed/cisplatin, has

limited benefit. In a phase III trial, treatment with pemetrexed/cisplatin improved survival compared to cisplatin alone from 9 to 12 months.[1] Second-line chemotherapy has no proven benefit.[2] In order to develop the targeted therapies necessary to radically alter the clinical course of MM, it is important to identify the oncogenic mutations and signaling pathways that drive its development and sustain its maintenance.[3]

NF2 mutations

About 75% of MMs carry inactivating mutations in the tumor suppressor gene NF2. Mutations at the BAP1 locus are also frequent in MM but appear to be mutually exclusive with NF2 mutations.[4] From our MSK-IMPACT data, we are identifying NF2 alterations in about 40% of patients. NF2 was first identified in 1993 as the gene responsible for Type II familial Neurofibromatosis, a rare, autosomally dominant inherited disease that causes central nervous system tumors such as Schwannomas, meningiomas, and ependymomas. Since that time, NF2 mutations or loss of function have been identified in several other malignancies including mesothelioma and a small percentage of renal cell, cervical and bladder cancers. Althoughwe have known about NF2 for 20 years, the mechanismby which it suppresses tumor formation until recently has remained unclear.[5]

NF2 encodes for the FERMdomain protein Merlin, which is homologous to the ERM proteins Ezrin, Radixin, and Moesin. The function of canonical ERM proteins is to mediate association of various membrane receptors with the actin cytoskeleton. Merlin has homology with other ERM proteins with the presence of a FERM domain, an α-helical domain, and a C-terminal domain. However, canonical ERM proteins have an actin-binding motif in their C-terminal domain, which is not present in Merlin, whereas Merlin has a unique N-Terminal extension. ERM proteins are maintained in a dormant state by association of the FERM domain with the C-terminal domain resulting in a “closed” conformation. With activation of Rho, its target Rho-kinase phosphorylates the actin binding motif, disrupting its association with the FERM domain. The newly generated “open” conformer associates through its FERM domain with the cytoplasmic segment of cell adhesion molecules, whereas the C-terminal actin binding motif interacts with actin filaments, regulating the organization of the cytoskeleton. In contrast, Merlin’s C-terminal domain is phosphorylated by PAK at Ser 518, resulting in inactivation of the growth suppressor activity of the protein.[5] Cell-to-cell contact, mediated by cadherins, or loss of matrix adhesion, mediated by integrins, inactivates PAK, leading to the accumulation of the de-phosphorylated, growth inhibitory form of Merlin.[6] We have recently discovered that the de-phosphorylated, active conformer of Merlin translocates into the nucleus, where it binds to the pro-oncogenic E3 ubiquitin ligase CRL4DCAF1, inhibiting its ability to ubiquitylate target proteins.[7] Notably, Merlin inhibits CRL4DCAF1, which in turn promotes a broad oncogenic gene expression program, which includes targets of the oncogenic transcriptional co-activator YAP. Genetic epistasis experiments and an analysis of several Merlin missense mutations from NF2 patients have demonstrated that the de-phosphorylated form of Merlin suppresses tumorigenesis by inhibiting CRL4DCAF1.[7]

Cullin-RING finger ligases (CRLs)

CRLs make up the largest family of ubiquitin ligases in eukaryotic cells. CRL4 ligase complexes are comprised of the Cul4 scaffold, with the N-terminal segment associating -

via the adaptor DDB1 - to one of several (>50) specific substrate receptors (DCAFs), and the C-terminal domain interacting with Rbx1 and the E2 ubiquitin-conjugating enzyme.[8,9] All known CRL4 ubiquitin ligases are nuclear and regulate cell proliferation, survival, and DNA repair by ubiquitinating transcription factors, histones, or chromatin remodeling enzymes.[10] However, no physiological target of CRL4DCAF1 has been identified until recently. In our Preliminary Studies, we found that de-repressed CRL4DCAF1 functions in the nucleus to suppress the output of Hippo signaling. Mechanistically, CRL4DCAF1 binds directly to the tumor suppressor kinases Lats1 and 2 and directs their conjugation to ubiquitin. Whereas Lats1 is poly-ubiquitylated and targeted for proteasomal-dependent degradation, Lats2 is oligo-ubiquitylated at multiple sites, resulting in both cases in loss of kinase activity. As a consequence, the transcriptional co-activators and oncogenes, YAP and TAZ, which are inactivated by Lats 1 and 2, become active and function redundantly to support the ability of NF2 mutant cells to proliferate under standard culture conditions, to form colonies in soft agar, and to form tumors in mice. These results indicate that de-repressed CRL4DCAF1 promotes tumorigenesis by inhibiting the tumor suppressor Lats1 and 2, thus unleashing YAP/TAZ and TEAD-dependent transcription.[11] These results reveal the molecular underpinnings of the tumor suppressor function of Merlin. Intriguingly, LATS1 and 2 are mutated in ~ 8% of MM cases and this subset of tumors does not include NF2 mutations.[12] Hence, the tumor suppressor pathway we have identified appears to be inactivatedin ~ 83% of MM cases.

Strategies for inhibiting oncogenic signaling in NF2 mutant MM

We have previously shown that inactivation of Merlin leads to constitutive activation of mTORC1 in MM cells, and these cells are particularly sensitive to rapamycin.[13] This finding led to a phase II trial that we opened at MSK testing everolimus in patients with previously treated MM using NF2 as a biomarker. Unfortunately that trial closed early due to loss of funding from the sponsor; a SWOG trial with everolimus was completed but did not meet the prespecified PSF endpoint.[14] Other trials with dual PI3K/mTOR inhibitors, such as GDC0980, have shown promising activity[15], presumably because these inhibitors block mTOR more effectively relative to rapalogs, and at the same time prevent the negative feedback loops which lead to activation of PI3K in cells treated with rapalogs.[16] We reason, however, that MM cells display activation of multiple signaling pathways as a result of activation of CRL4DCAF1 and YAP/TEAD-dependent gene expression. To block activation of all these pathways, it is necessary to target upstream oncogenic signaling via inhibition of CRL4DCAF1. Conjugation of the ubiquitin-like protein NEDD8 to cullin is required for the assembly of active CRL complexes.[17] Takeda has developed a potent and selective inhibitor of the NEDD8-activating enzyme, pevonedistat, which exhibits antitumor activity in xenograft models.[18]

Pevonedistat

Pevonedistat (TAK-924, formerly MLN4924) is a first-in-class small molecule inhibitor of NAE. Inhibition of Nedd8-activating enzyme (NAE) stabilizes a subset of the proteins that

are also stabilized by inhibition of the proteasome. Pevonedistat exhibits potent *in vitro* cytotoxic activity against a variety of human tumor-derived cell lines in which cell death was shown to correlate with NAE inhibition. In most cancer cell lines studied, including those derived from lung, colon, and lymphoma tissues, the mechanism of cell death appeared to be a consequence of uncontrolled DNA synthesis in the S phase of the cell cycle followed by a DNA-damage response and induction of cell death However, in the NF- · B-dependent lymphoma line, OCI-Ly10, apoptosis was observed following a G1 arrest suggesting that there may be multiple consequences of NAE inhibition that lead to cell death depending on the genetic background of the malignant cells. Hematologic and nonhematologic xenograft models support that inhibition of NAE activity may target a broad range of tumors.

Preclinical efficacy of the CRL inhibitor pevonedistat

Pevonedistat is a potent and selective inhibitor of NAE activity (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 treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines derived from acute leukemias, lymphomas, multiple myeloma, and a range of solid tumor types. Changes in protein levels observed in cultured cells treated with 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 NFE2-related factor 2 (Nrf2) and chromatin-licensing and DNA-replication factor-1 (Cdt-1). In most cell lines evaluated, NAE inhibition by 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. When administered in combination with hypomethylating agents azacitidine and decitabine demonstrated synergistic activity in AML cell lines.

Pevonedistat demonstrated pharmacodynamic and antitumor activity in solid tumor, lymphoma, and AML xenograft models when administered to immunocompromised mice by the subcutaneous (SC) route. Antitumor activity of pevonedistat in mice bearing HL-60 and THP-1 tumor xenografts was enhanced by combination treatment with azacitidine. Combination treatment with 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 pevonedistat and carboplatin in both NCI-H69 human small cell lung cancer (SCLC) xenografts and LU1143 primary sqNSCLC xenografts resulted in significant antitumor activity.

In vitro assay results indicated a low risk for human ether-à-go-go related gene (hERG) channel inhibition by pevonedistat or its 3 major circulating metabolites. In a Good Laboratory Practices (GLP)-compliant cardiovascular safety pharmacology assessment in male beagle dogs dosed via intravenous (IV) infusion at 15, 30, or 40 mg/kg (300, 600, or 800mg/m^2, respectively), pevonedistat was not well tolerated at doses ≥30 mg/kg (≥600mg/m^2). Mortality and/or moribundity were observed within 24 hours postdose as a result of gastrointestinal 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.

The dose-limiting toxicities (DLTs) in the 2-cycle studies for rats and dogs were gastrointestinal toxicity and bone marrow and lymphoid tissue depletion. Most adverse effects were resolving or had resolved after a 2-week recovery period. Pevonedistat did not result in lethality in either of the 5-cycle studies. 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; and in males, vacuolation and degeneration of the seminiferous epithelium of the testes. Most adverse effects were reversing or had reversed aftera 2-week recovery period in both rats and dogs. Given that there were prominent effects on testes and ovaries noted at all doses tested in the GLP-compliant repeat-dose toxicology studies in both dogs and rats, pevonedistat likely represents a substantial reproductive and developmental hazard. Pevonedistat was not mutagenic in the bacterial reverse mutation assay (Ames assay).

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, pevonedistat is predominantly metabolized by the cytochrome P450 (CYP) isozyme 3A4. There is potential for drug drug interactions (DDIs) if pevonedistat is coadministered with drugs that are CYP3A inhibitors or inducers. Pevonedistat is neither an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC_{50} > 100 µM and Ki > 50 µM) nor an inducer of CYP1A2, 2B6, or 3A4/5 (at concentrations up to 30 µM), but is a weak inhibitor of CYP2B6 and 2C8 (IC_{50} = 97.6 and 23.1 µM, respectively). The major elimination pathway of pevonedistat in animals is through the hepatic route. Pevonedistat is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) in Caco 2 cells. Pevonedistat is also a weak inhibitor of P-gp (IC_{50} = 41.2 to 56.0 µM) and BCRP (IC_{50} = 6.3 µM), but not of MRP2 (IC_{50} > 200 µM). Additionally, pevonedistat is not a substrate for organic anion-transporting proteins (OATPs).

Detailed information regarding the nonclinical pharmacology and toxicology of pevonedistat is provided in the Investigator's Brochure (IB).

<u>Preclinical efficacy of the CRL inhibitor pevonedistat in MM</u>

To investigate the potential efficacy of the NEDD8-Activating Enzyme inhibitor, pevonedistat, in *NF2* mutant tumor cells, we selected the *Nf2*$^{-/-}$ FC-1801 mouse Schwannoma cells, which were generated by infecting primary mouse Schwann cell cultures from E12.5 *Nf2*$^{f\ lox/flox}$ embryos with adenoviral Cre [19], and a panel of *NF2* mutant MPM cells, which we have previously characterized.[20] We have previously shown that silencing of DCAF1 inhibits the ability of *NF2* mutant MPM Meso-33 cells to grow in soft agar and suppresses the capacity of FC-1801 Schwannoma cells to form benign tumors upon subcutaneous injection in nude mice [7]. We found that 0.5-1 micromolar pevonedistat completely suppresses conjugation of NEDD8 to total Cullin 4 in both FC-1801 and Meso-33 cells (IC_{50} ~ 0.1 micromolar). Provocatively, significantly lower concentrations of the drug were sufficient to block NEDD8 conjugation to the fraction of Cullin 4 associated with $CRL4^{DCAF1}$ in both types of cells, suggesting that $CRL4^{DCAF1}$ is especially sensitive to pevonedistat. Furthermore, *in vivo* ubiquitylation assays demonstrated that 0.5 micromolar pevonedistat efficiently inhibits the E3 ligase activity of $CRL4^{DCAF1}$. As anticipated from our

observation that $CRL4^{DCAF1}$ inhibits Lats1 and 2, pevonedistat activated Lats1/2 and thereby induced accumulation of the phosphorylated and inactive form of its target oncoprotein YAP in Meso-33 cells. In addition, pevonedistat blocked TOR signaling in *NF2* mutant cells, suggesting that that de-regulated $CRL4^{DCAF1}$ also drives the expression of genes that overactivate TOR in these cells. Finally, the drug inhibited phosphorylation of Rb and histone H3 and induced accumulation of p27. These results indicate that pevonedistat blocks the oncogenic signaling pathways activated by loss of *NF2*, inducing cell cycle arrest. We next evaluated the ability of pevonedistat to inhibit the proliferation of *NF2* mutant mesothelioma cells *in vitro*. Notably, MTT assay indicated that 0.5-1 micromolar pevonedistat completely inhibits the proliferation of four *NF2* mutant mesothelioma cell lines, which do not harbor additional mutations at the *BAP1* tumor suppressor locus [Meso-33, JMN, H2052, VAMT; [20,21]]. In contrast, 5 micromolar pevonedistat did not exert an inhibitory effect on two *NF2* mutant mesothelioma cell lines carrying additional mutations at the *BAP1* locus [Meso-9 and Meso-10; [20,21]], suggesting that the presence of additional oncogenic mutations may influence the sensitivity of *NF2* mutant tumor cells to pevonedistat. Importantly, treatment of several NF2 mutant MPM cell lines with 0.5 micromolar pevonedistat significantly increased their sensitivity to pemetrexed or cisplatin. Interestingly, xenograft studies indicated that pevonedistat at 90 mg/kg Q2Dx3/week significantly inhibits the ability of the *NF2* mutant VAMT cells to grow as subcutaneous tumors in NOG mice, but did not induce tumor regression (n=6; $P<0.001$).

To examine the in vivo efficacy of pevonedistat in combination with pemetrexed/cisplatin, we conducted xenograft studies. We have an MTA in place and have obtained large quantities of pevonedistat required for in vivo studies. In addition, we have an ongoing collaboration with Takeda and thus have access to the pharmacokinetics and pharmacodynamics properties as well as toxicity profiles of pevonedistat in various strains of mice. Based on their experience, we have selected doses and schedules of administration of the drug that inhibit neddylation of Cullins in vivo without causing toxicity.

Clinical experience with pevonedistat

The clinical development program of pevonedistat began with 4 phase 1 studies of single agent pevonedistat at doses ranging from 25 to 278 mg/m^2:

- Study C15001 in patients with solid tumors.
- Study C15002 in patients with lymphoma or multiple myeloma.
- Study C15003 in patients with AML, high-grade myelodysplastic syndrome (MDS), or acute lymphoblastic leukemia (ALL).
- Study C15005 in patients with melanoma.

In these studies, toxicity involving multi organ failure on C1D1, including serious adverse events (SAEs) of renal, hepatic, and cardiac failure, some with a fatal outcome, was identified at doses equal to or above 110 mg/m^2. 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 pevonedistat program in October 2012. The current understanding

of the renal toxicity observed with 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.

As of January 2016, approximately 180 additional patients were treated in single agent and combination studies, and no C1D1 SAEs of multi-organ failure as described above have been observed. These patients received pevonedistat at a dose of 50 to 100 mg/m^2 as a single agent, a dose of 15 to 30 mg/m^2 in combination with different standard of care therapies, or a dose of 8 mg/m2 to 20 mg/m^2 in combination with a CYP3A inhibitor.

Current development is focused on pevonedistat in combination with standard clinically available therapies in hematologic malignancies and solid tumors. Two phase 1b clinical studies are closed to enrollment but are still ongoing with active patients:

- Study C15009 (phase 1b) evaluated the maximum tolerated dose (MTD) of 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 [11].
- Study C15010 (phase 1b) evaluated the MTD of pevonedistat plus docetaxel, gemcitabine, or the combination of carboplatin and paclitaxel, in patients with solid tumors [12-13].

Additionally, Study C15011 (phase 1) is evaluating the effects of CYP3A mediated inhibition of pevonedistat in patients with solid tumors (DDI assessment; Part A). After completion of the DDI assessment portion of the study, patients have the opportunity to continue in the study by participating in Part B (pevonedistat plus docetaxel or the combination of carboplatin and paclitaxel).

The cumulative enrollment in all clinical studies through 22 January 2016 is approximately 390 patients (defined as having received at least 1 dose of study drug).

Two studies are currently enrolling:

- Study 2001: A Phase 2, randomized, controlled Open-Label Clinical study of the efficacy and safety of Pevonedistat plus Azacitidine versus single-agent azacitidine in patients with higher-risk myelodysplastic syndromes, chronic myelomonocytic leukemia and low-blast acute myelogenous leukemia.
- Study 1012: A phase 1/1b, Open-label Study of Pevonedistat (MLN4924, TAK-924) as Single Agent and in Combination with Azacitidine in adult East Asian patients with acute myeloid leukemia or myelodysplastic syndromes.

<u>Pharmacokinetics</u>

The clinical pharmacokinetics (PK) of pevonedistat have been evaluated in 4 monotherapy phase 1 studies in 96 patients with solid tumors (C15001 and C15005) and 109 patients with hematologic malignancies (C15002 and C15003). These studies have evaluated the

single- and multiple-dose PK of 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 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. Mean terminal disposition t1/2z was estimated to be approximately 10 hours (range 7.7-15.2) across doses and schedules. Consistent with in vitro data, 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. Pevonedistat generally exhibited linear PK over the dose range studied. Observed interindividual variability (IIV) was generally moderate with 18% to 41% coefficient of variation (CV) for maximum concentration (Cmax), 12% to 56% CV for area under the plasma concentration-time curve from time zero to 24 hours postdose (AUC_{24}), and 15% to 33% CV for the area under the plasma concentration-time curve from time zero to the end of the dosing interval when pevonedistat was administered on Days 1, 3, and 5. Body size influences pevonedistat systemic clearance andvolume of distribution, thus supporting body surface area (BSA)-normalized dosing to reduce variation in systemic exposure of pevonedistat in cancer patients. Pevonedistat clearance 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 creatinine clearance > 30 mL/min) on pevonedistat PK.

Additionally, evaluation of pevonedistat PK is ongoing for 2 studies of pevonedistat in combination with different standard-of-care therapies, and for a DDI study evaluating the effects of CYP3A mediated inhibition on pevonedistat. 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 pevonedistat in the presence of docetaxel or gemcitabine have been observed whereas a trend towards increasing plasma concentrations of pevonedistat in the presence of carboplatin + paclitaxel was evident. This apparent drug interaction effect, which cannot be explained at this time, warrants further understanding of the disposition properties of pevonedistat in humans. Lastly, multiple doses of fluconazole, a moderate CYP3A inhibitor, had minimal effect (13% increase in mean area under the plasma concentration time curve from zero to infinity [AUC_{inf}]) on the single-dose IV PK of pevonedistat, while pevonedistat systemic exposure increased by 23% on average in the presence of the strong CYP3A inhibitor, itraconazole.

Pharmacodynamics

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

Rationale for clinical trial design

To test the efficacy and safety of pevonedistat in patients with pleural or peritoneal MM, we will conduct this single institution clinical trial comprised of two cohorts: 1) a phase II trial to assess the clinical benefit rate of single agent pevonedistat in patients with NF2 mutant MM, and 2) a phase I trial to establish the safety of combining pevonedistat with pemetrexed/cisplatin in previously untreated patients.

Cohort 1 will assess the clinical activity of pevonedistat as a single agent in patients selected for NF2 mutations. This cohort will enroll patients with pleural or peritoneal mesothelioma MM with progression of disease after prior treatment with one or two prior chemotherapy regimens. There are no approved therapies for these patients, and the response rate of standard chemotherapy is negligible.[2] Patients will typically have MSK IMPACT performed for molecular phenotyping while they are receiving first-line therapy (testing takes several weeks), and so we will be able to select patients for this cohort whose tumors demonstrate NF2 mutations. Based on the preclinical data described above showing growth inhibition with pevonedistat as a single agent, we are interested in also including disease stabilization in the efficacy assessment. Thus, the primary endpoint of this cohort will be clinical benefit rate (CBR) as measured by complete or partial response or stable disease at 18 weeks (6 cycles).

Cohort 2 will assess the combination of pevonedistat with chemotherapy, which is of particular interest given the data described in the preliminary studies. Cohort 2 will enroll patients with previously untreated, unresectable, pleural or peritoneal MM. Because of the time required to obtain molecular genotyping, these patients will not be selected up-front for NF2 mutations, but MSK IMPACT will be performed during the courseof their therapy.Since there are no clinical data regarding the combination of pevonedistat with pemetrexed/cisplatin, the primary endpoint will be to assess safety, and establish a recommended phase II dose.

If activity is demonstrated in the single-agent cohort, and safety demonstrated in the combination cohort, we would propose a subsequent multicenter, randomized phase II trial of pemetrexed/cisplatin +/- pevonedistat.

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

This study is a single institution trial with two cohorts to test the efficacy of the NEDD8 inhibitor, pevonedistat, as a single agent in patients with NF2 mutant MM (Cohort 1), and also to test the safety of pevonedistat in combination with standard chemotherapy, pemetrexed/cisplatin (Cohort 2).

4.3 Intervention

Cohort 1: This cohort will enroll patients with advanced MM previously treated with 1-2 prior chemotherapy regimens. Patients in this cohort must have tumors with NF2 mutations as previously determined by any CLIA lab certified NGS platform. Patients will receive single agent pevonedistat at the recommended phase II dose of 50 mg/m^2 IV days 1, 3, 5 in 21-day cycles. Patients will be assessed for toxicity on day 1 of each cycle. Patients will undergo imaging after every two cycles to assess response. The primary endpoint is the clinical benefit rate (CBR) defined as CR + PR + SD at 18 weeks (6 cycles). As an exploratory endpoint, the first 10 patients in this cohort will have on-treatment core biopsies performed one to two weeks after starting therapy to obtain tissue for confirmation of expected drug effects.

Cohort 2: This cohort will enroll patients with advanced MM previously untreated with chemotherapy. There will be no genotyping restriction for enrollment of these patients, but MSK-IMPACT will be performed while they are receiving therapy. Patients will receive pemetrexed/cisplatin at the standard doses. Pevonedistat will be given in dose escalation groups using a 3+3 design. The starting dose will be 15 mg/m^2 days 1, 3, 5, followed by escalation to 20 and 25 mg/m^2 or de-escalation to 10 mg/m^2. Patients will receive up to 6 cycles of pemetrexed/cisplatin + pevonedistat, and following that will be treated with pevonedistat alone (maintenance therapy) until progression. Patients will be assessed for toxicity weekly with cycle 1, and then on day 1 of each subsequent cycles. Criteria for dose limiting toxicities (DLTs) are described in Section 11.0. The primary endpoint of this cohort is to establish the safety and the recommended phase II dose of this combination.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

Pevonedistat

The drug product is labeled Pevonedistat (TAK-924/MLN4924) Concentrate for Solution for Infusion. Pevonedistat injection drug product formulation consists of 10 mg/mL (as free base) of pevonedistat HCl in an aqueous solution of 7.45 mg/mL citric acid (anhydrous), 3.29 mg/mL trisodium citrate dihydrate, and 100 mg/mL ß-Cyclodextrin sulfobutyl ether (Captisol®) at pH 3.3. Each USP Type I glass vial nominally contains 5 mL of compounded sterile solution, sealed with a Teflon®-coated butyl rubber stopper and oversealed with an aluminum seal and a plastic cap.

Full details are available in the IB.

Preparation, Reconstitution, and Dispensation

Pevonedistat (TAK-924/MLN4924) is acytotoxic anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling pevonedistat.

The specified number of pevonedistat Injection Drug Product vials should be removed and allowed to equilibrate to room temperature prior to dilution. The vial must not be shaken at any time during dose preparation.

Using aseptic technique, the appropriate volume of drug should be withdrawn from vial(s), then injected into a 250-mL IV bag containing 5% dextrose solution, and then gently inverted repeatedly to mix. The pevonedistat prepared IV bag must be used within 6 hours (time to the end of an injection) if stored at ambient temperature. Alternatively, the prepared IV bag is chemically stable and may be stored for up to 18 hours at 2˚C to 8˚C. After 18 hours of storage at 2˚C to 8°C, the prepared IV bag must be used within 3 hours (time to the end of an injection) upon coming to ambient temperature.

The bag, needle, and syringe must be disposed of in a proper biohazard container.

Packaging and Labeling

Pevonedistat (TAK-924/MLN4924) will be provided in 10-mL glass vials at a concentration of 10 mg/mL.

Storage, Handling, and Accountability

Vials of pevonedistat (TAK-924/MLN4924) are to be stored at 2°C to 8°C. Pevonedistat injection is stable at ambient temperature for 8 hours before dilution. All investigational supplies are to be kept in a secure area with controlled access.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The amount of drug to be administered will be based on body surface area (BSA). BSA will be calculated using a standard nomogram on Cycle 1, Day 1 (see Appendix), and at subsequent visits if the patient experiences a > 5% change in body weight from the weight used for the most recent BSA calculation.

The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, and total drug administered in milliliters and milligrams.

All patients will receive pevonedistat diluted with 5% dextrose in a 250-mL IV bag via IV infusion via a 60-minute IV infusion. Pevonedistat should be administered through central or peripheral venous access. The infusion may be slowed or stopped and restarted for any associated infusion-related reactions. All infusion times must be recorded. The total time from drug reconstitution to end of infusion must not exceed 6 hours. Doses of pevonedistat must be separated by at least 1 full calendar day.

Drug accountability: All study drug supplies must be kept in a locked room with limited access. The study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or other site personnel supply study drug to other investigators, patients, or clinic, or allow supplies to be used other than directed by this protocol without prior authorization from Takeda. The pharmacist will maintain a complete drug accountability record with lot numbers, the dates drug was dispensed, and the dose of pevonedistat the patient received. The prescribed dose should also be recorded in the patient's medical records. At the conclusion of the study, all unused pevonedistat will be destroyed on-site as described in a standard operating procedure for the destruction of chemotherapeutic waste.

Pemetrexed:

Pemetrexed (Alimta®, Eli Lilly) is a commercially available medication with a complete description of the drug, its clinical pharmacology, contraindications, warnings, precautions and adverse reactions available in the package insert. Pemetrexed will be administered as per institutional guidelines.

Cisplatin:

Cisplatin (Platinol®, Bristol Myers) is a commercially available medication with a complete description of the drug, its clinical pharmacology, contraindications, warnings, precautions and adverse reactions available in the package insert. Cisplatin will be administered as per institutional guidelines.

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

Patients must meet all of the following criteria for eligibility:

6.2 Subject Inclusion Criteria

Both cohorts:

- Patients must have a histologically confirmed diagnosis of epithelioid, sarcomatoid, or mixed-type malignant pleural or peritoneal mesothelioma that is not amenable to surgery.
- Patients must have measurable disease according to the modified RECIST criteria for pleural mesothelioma, or standard RECIST for peritoneal mesothelioma.
  Patients must have adequate tissue sample available for molecular profiling with MSK-IMPACT (archived tissue block or 15-20 unstained slides). Patients will sign a separate informed document (IRB #12-245) to allow this to be performed.
- Patients must be at least 18 years of age.
- Karnofsky performance status $\geq$ 70%.
- Adequate renal function: serum creatinine ≤ 1.5 x ULN.
- Clinical laboratory values within the following parameters (repeat if more than 7 days before the first dose):
  - Albumin > 2.7 g/dL
- Patients must have adequate hepatic function as defined by:
  - AST and ALT ≤ 2.5 x ULN
  - Total bilirubin ≤ upper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5 x ULN of the direct bilirubin.
- Patients must have adequate bone marrow function as defined by:
  - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L
  - Platelets ≥ 100 x 10^9/L
  - Hemoglobin ≥ 9 g/dL.
- Female patients who
  - Are postmenopausal (see Appendix for definition) for at least 1 year before the screening visit, OR

- Are surgically sterile, OR
- If they are of childbearing potential:
  - Agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see Appendix), at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug (female and male condoms should not be used together), or
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

- Male patients, even if surgically sterilized (i.e., status post vasectomy), who:
  - Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug (female and male condoms should not be used together), or
  - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)
- Signed informed consent

Cohort 1:

- Patients must have received at least one and no more than four prior systemic therapy regimens. At least one of the regimens must have included pemetrexed and a platinum.
- Patients must have MM that harbors an NF2 mutation believed to cause functional loss of the NF2 protein as determined by any CLIA lab certified NGS platform or NF2 loss must be documented by CLIA certified IHC.

Cohort 2:

- Patients must not have previously received treatment with chemotherapy for MM.
- Patients must not have ≥ grade 2 peripheral neuropathy.
- Patients must not have > grade 2 hearing deficits.

6.3 Subject Exclusion Criteria

- Patients currently receiving anticancer therapies or who have received anticancer therapies within 3 weeks of the start of study drug including chemotherapy, biologics, targeted therapies, or immunologics.
- Treatment with any investigational products within 4 weeks before the first dose of any study drug.
- Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures.

- Patients currently receiving radiation therapy, or who have received radiation within 2 weeks from the start of therapy.
- Patients who have had a major surgery or significant traumatic injury within 4 weeks of start of study drug, patients who have not recovered from the side effects of any major surgery (defined as requiring general anesthesia) or patients that may require major surgery during the course of the study.
- 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 nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone resection.
- Life-threatening illness unrelated to cancer.
- Patients with uncontrolled coagulopathy or bleeding disorder.
- Patients who have any severe and/or uncontrolled medical conditions or other conditions that could affect their participation in the study such as:
    - Known cardiopulmonary disease defined as:
        - Unstable angina
        - Congestive heart failure (New York Hear Association [NYHA] Class III or IV
        - Myocardial infarction (MI) within 6 months prior to first dose (patients who had ischemic heart disease such as ACS, MI and/or revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll).
        - Cardiomyopathy
        - Clinically significant arrhythmia:
            - Polymorphic ventricular fibrillation or torsade de pointes.
            - Permanent atrial fibrillation [a fib], defined as continuous a fib ≥ 6 months.
            - Persistent a fib, defined as sustained a fib lasting > 7 days and/or requiring cardioversion in the 4 weeks before screening
            - Grade 3 a fib defined as symptomatic and incompletely controlled medically, or controlled with device (e.g. pacemaker), or ablation
            - Patients with paroxysmal a fib or < Gr 3 a fib for period of at least 6 months are permitted to enroll provided that their rate is controlled on a stable regimen.
            - Implantable cardioverter defibrillator
        - Moderate to severe aortic and/or mitral stenosis or other valvulopathy (ongoing)
        - Symptomatic pulmonary hypertension
    - Active infection requiring IV antibiotic, antiviral, or anti-fungal medications within 2 weeks of starting study drug.
    - Known history of HIV seropositivity
- Known 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.

- Known hepatic cirrhosis or severe pre-existing hepatic impairment
- Uncontrolled high blood pressure (i.e., systolic blood pressure > 180 mm Hg, diastolic blood pressure > 95 mm Hg).
- Prolonged rate corrected QT (QTc) interval ≥500 msec, calculated according to institutional guidelines.
- Left ventricular ejection fraction (LVEF) < 50% as assessed by echocardiogram or radionuclide angiography.
- Known central nervous system (CNS) involvement.
- Female patients who are both lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.
- 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).
- Male patients who intend to donate spermduring the courseof this study or 4 months after receiving their last dose of study drug(s).
- Patients with a currently active second malignancy requiring treatment.
- Treatment with clinically significant metabolic enzyme inducers within 14 days before the first dose of the study drug. Clinically significant metabolic enzyme inducers are not permitted during this study.

7.0 RECRUITMENT PLAN

Eligible patients with MM will be recruited from the Thoracic Oncology Service at MSKCC among patients that are cared for at that institution or through referrals. Every attempt will be made to recruit women and minorities in this study. Participation is voluntary. The consenting physician will inform patients of their diagnosis, current treatment options, including standard treatment, and the risks, benefits and experimental nature of this treatment program. Patients under the age of 18 are excluded because this disease does not occur in patients that age, and the safety of these treatments has not been established for them. There are no gender or racial restrictions.

8.1 PRETREATMENT EVALUATION

To be completed within 14 days of initiating treatment:

- Updated history
- Physical examination including vitals signs, weight, and performance status
- Concomitant medications
- Complete blood count (CBC)
- Comprehensive panel
- Pregnancy test (for women of childbearing potential)
- ECG

- Echocardiogram (for patients who have not had this performed within 1 year)
- CT scan of chest and any other relevant sites of disease (within 28 days)
- Urinalysis with microscopic analysis

9.1 TREATMENT/INTERVENTION PLAN

Cohort 1:

Patients in Cohort 1 will be treated with single-agent pevonedistat. Pevonedistat will be administered as an IV infusion at a dose of 50 mg/m^2 days 1, 3, and 5 of a 21-day cycle. Treatment will be administered as an outpatient. Patients will be evaluated prior on day 1 of each cycle for toxicity assessment. CT scans will be performed to assess for response every 6 weeks (2 cycles).

Cohort 2:

Patient in Cohort 2 will be treated with pevonedistat in combination with pemetrexed and cisplatin. Pemetrexed, 500 mg/m^2 and cisplatin, 75 mg/m^2, will be given at fixed doses on day 1 of each cycle. Folic acid 800 mcg will be given daily at least 5 days prior to the first dose of pemetrexed and continued daily until 3 weeks after the last dose of pemetrexed. Vitamin B12 1000 mcg will be administered as an intramuscular injection approximately 1 week prior to the first dose of pemetrexed and repeated approximately every 9 weeks until 3 weeks after the last dose of pemetrexed. Anti-emetics will be administered per institutional guidelines. Dexamethasone 12 mg will be given for days 2 and 3 after cisplatin administration. Patients will be instructed to drink 1-2 liters of fluid the night prior to chemotherapy and will be given >1000 mL D5W or normal saline over 1-2 hours before and after cisplatin administration. Patients will receive a bolus of mannitol 12.5 grams prior to cisplatin administration. Patients will receive up to 6 cycles of pemetrexed/cisplatin + pevonedistat, and following that will be treated with pevonedistat alone (maintenance therapy) until progression. CT scans will be performed to assess for response every 6 weeks (2 cycles).

Pevonedistat will be given in a 3-by-3 dose escalation based on the table below:

Dose level	Dose
-1	10 mg/m^2 days 1, 3, 5
0	15 mg/m^2 days 1, 3, 5
1	20 mg/m^2 days 1, 3, 5
2	25 mg/m^2 days 1, 3, 5

Patients in Cohort 2 will be assessed weekly in the first cycle to assess for toxicity.

The initial 3 patients of each cohort must complete cycle 1 prior to making a decision regarding dose escalation. If none of the 3 patients at dose level 0 has a dose-limited toxicity (DLT, as defined in Section 11.0), the dose level will be escalated. If one has a DLT that dose level will be expanded with 3 more patients. Dose escalation will stop if ≥2 DLTs are seen at a dose level. The MTD is defined as the highest dose level at which no more than 1 of the 6 patients at that level has a DLT. If no patient in the 3-patient cohort has a DLT and the dose level is under final consideration for the MTD, an additional three patients will be treated at that level for confirmation.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

COHORT 1*	Baseline[1]	Cycle 1					Cycle 2			Cycle 3 and beyond			EOT
		Day 1	Day 2	Day 3	Day 5	Day 8 & 15	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	
Informed consent	X												
Pathology sample for MSK-IMPACT (if not already performed)	X												
History, physical exam, performance status	X	X					X			X			X
Vital Signs	X	X		X	X		X	X	X	X	X	X	X
Adverse events monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC	X	X		X	X	X	X			X			X
Comprehensive panel[2]	X						X			X			X
Select chemistry panel[3]		X		X	X	X		X	X		X	X	
PT and aPTT	X	X					X			X			
Serum pregnancy test (for women of childbearing potential)	X												
Serum or urine pregnancy test (for women of childbearing potential)		X					X			X			
ECG[4]	X	X		X	X								X
Echocardiogram[5]	X												
Urinalysis with microscopic analysis[6]	X												
CT chest and other relevant disease sistes[7]	X									X			
Pevonedistat administration		X		X	X		X	X	X	X	X	X	
Tumor Biopsy[8]						X (D15 only)							

.* All assessments (including pevonedistat administration) will be performed with a window of +/- 3 days.
[1] Within 14 days of starting therapy, except for CT scan which can be within 28 days.
[2] Includes electrolytes, BUN/creatinine, sodium, potassium, chloride, carbon dioxide, glucose, urate, total bilirubin, direct bilirubin, ALP, LDH, AST, ALT, albumin, magnesium, phosphate and calcium.
[3] Includes BUN, creatinine, phosphate, total bilirubin, albumin, ALP, AST, and ALT
[4] ECG to be performed after infusion and subsequently as needed
[5] Patients who have not had this performed within 1 year
[6] Urinalysis will include assessments of turbidity and color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, glucose, and leukocyte esterase. Urine microscopic analysis will include erythrocytes, leukocytes, bacteria, casts, and crystals.
[7]CT scan will be performed at the completion of every 2 cycles (i.e. every 6 weeks).
[8]First 10 patients from cohort 1. Day 15 +/-7 days. See below for description of correlative studies.

COHORT 2*	Base-line[1]	Cycle 1					Cycle 2			Cycle 3 and beyond			EOT
		Day 1	Day 2	Day 3	Day 5	Day 8 & 15	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	
Informed consent	X												
History, physical exam, performance status	X	X				X	X			X			X
Vital Signs	X	X		X	X	X	X	X	X	X	X	X	X
Adverse events monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X
CBC	X	X		X	X	X	X			X			X
Comprehensive panel[2]	X						X			X			X
Select chemistry panel[3]		X		X	X	X		X	X		X	X	
PT and aPTT	X	X				X	X			X			
Serum pregnancy test (for women of childbearing potential)	X												
Serum or urine pregnancy test (for women of childbearing potential)		X					X			X			
ECG[4]	X	X		X	X								X
Echocardiogram[5]	X												
Urinalysis with microscopic analysis[6]	X												
CT chest and other relevant disease sites[7]	X									X[6]			
Pevonedistat administration		X		X	X		X	X	X	X	X	X	
Pemetrexed/ cisplatin administration[8]		X					X			X			

PK assessment[9]		X	X	X									

* All assessments (including pevonedistat administration) will be performed with a window of +/- 3 days.
[1] Within 14 days of starting therapy, except for CT scan which can be within 28 days.
[2] Includes electrolytes, BUN/creatinine, sodium, potassium, chloride, carbon dioxide, glucose, urate, total bilirubin, direct bilirubin, ALP, LDH, AST, ALT, albumin, magnesium, phosphate and calcium.
[3] Includes BUN, creatinine, phosphate, total bilirubin, albumin, ALP, AST, and ALT
[4] ECG to be performed after infusion
[5] Patients who have not had this performed within 1 year
[6] Urinalysis will include assessments of turbidity and color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, glucose, and leukocyte esterase. Urine microscopic analysis will include erythrocytes, leukocytes, bacteria, casts, and crystals.
[6] CT scan will be performed at the completion of every 2 cycles (i.e. every 6 weeks).
[8] Patients will receive up to 6 cycles of pemetrexed/cisplatin + pevonedistat, and following that will be treated with pevonedistat alone (maintenance therapy) until progression.
[9] PK draws: It is recommended that samples should be taken right after each infusion of pevonedistat before the infusion pump is turned off. However, there is a ± 10 minute window for Cycle 1 Day 1 PK draws and a ±2 hour window for Cycle 1 Day 2 and Day 3 PK draws. Samples should be collected in polypropylene nunc tubes. Please follow dosing schedule as outlined below:

Pharmacokinetics Schedule

Cycle and Day	Time point					
Cycle 1 Day 1	Pre-dose	End of infusion	1 hour post-infusion	2 hour post-infusion	4 hour post-infusion	6 hour post-infusion
Cycle 1 Day 2	24 hours post-infusion					
Cycle 1 day 3	48 hours post-infusion					

Correlative Studies: We will obtain on-treatment core biopsies from the first 10 patients in cohort 1 one to two weeks after starting therapy to obtain tissue for confirmation of expected drug effects. Levels of NEDD8-Cullin, YAP, and P-YAP will be measured by Western blot. Nuclearly localized (active) and cytoplasmic (inactive) YAP and TAZ will be assessed by immunohistochemistry in collaboration with Filipo Giancotti.

11.0 TOXICITIES/SIDE EFFECTS

NCI Common Terminology Criteria (CTC): This study will utilize the most recent version of the Common Terminology Criteria (CTC) version for toxicity and adverse event reporting (currently 4.0). A copy of the CTC can be downloaded from the CTEP home page (http://ctep.info.nih.gov). All treatment areas have access to a copy of the CTC.

Possible toxicities side effects

Pevonedistat

COMMON:

- Diarrhea
- Nausea
- Vomiting
- Fever
- Abnormal liver function tests
- Myalgias
- Musculoskeletal pain

OCCASIONAL

- Tachycardia
- Dehydration
- Electrolyte imbalance
- Myelosuppression

RARE AND SERIOUS

- Multi-organ failure
- Cardiac arrhythmia
- Kidney Failure
- Acute Phase response

Cisplatin (Group 2 only)

COMMON:

- Leukopenia
- Thrombocytopenia
- Anemia
- Mild hearing loss
- Hair loss
- Nausea, vomiting, constipation, or diarrhea
- Loss of appetite
- Changes in blood pressure
- Fatigue

OCCASIONAL

- Allergic reactions
- Kidney damage
- Neurologic abnormalities
- Peripheral neuropathy

- Liver irritation
- High blood pressure
- Weight loss
- Rash, skin changes
- Dehydration
- Electrolyte abnormalities
- Dyspnea or pneumonitis
- Mucositis
- Peripheral edema

RARE AND SERIOUS

- Thrombosis
- Vision changes
- Development of leukemia

Pemetrexed (Group 2 only)

COMMON:

- Leukopenia
- Thrombocytopenia
- Anemia
- Changes in blood pressure
- Temporary abnormalities in liver function tests
- Nausea, vomiting, constipation, or diarrhea
- Loss of appetite
- Fatigue

OCCASIONAL

- Allergic reactions
- Kidney damage
- Fever
- Weight loss
- Rash, skin changes
- Dehydration
- Electrolyte abnormalities
- Dyspnea
- Mucositis
- Peripheral edema

RARE AND SERIOUS

- Hemorrhage due to thrombocytopenia
- Severe anemia
- Kidney failure

Dose Delays and Modifications for Hematologic Toxicities

Hematologic Toxicity	Modification instructions
On day 1 of treatment: ANC < 1000/μL but ≥ 500/μL Or Platelet count < 100/μL but ≥ 50/μL	Hold treatment and recheck CBC weekly. Cohort 1: Resume pevonedistat at full dose once recovered. Cohort 2: Resume pevonedistat and pemetrexed/cisplatin at full dose. Add peg-filgrastim as per discretion of treating physician.
On day 1 of treatment: ANC < 500/μL Or Platelet count < 50/μL	Hold treatment and recheck CBC weekly. Cohort 1: Resume pevonedistat at next lower dose level once recovered. Cohort 2: Resume pevonedistat at next lower dose level once recovered. Administer pemetrexed at 400mg/m^2. Continue cisplatin at full dose 75 mg/m^2. Add peg-filgrastim as per discretion of treating physician.
Episode of febrile neutropenia at any time during last cycle	Hold treatment until resolution. Cohort 1: Resume pevonedistat at next lower dose level Cohort 2: Resume pevonedistat at next lower dose level once recovered. Administer pemetrexed at 400mg/m^2. Administer cisplatin at 60 mg/m^2. Add peg-filgrastim as per discretion of treating physician.

Dose Delays and Modifications for Nausea/Vomiting

Nausea/vomiting Grade	Modification instructions
At any time during the cycle: Grade 1	Both Cohorts: Maximize supportive care measures, e.g. ondansetron, lorazepam, dexamethasone, hydration. Proceed with full-dose treatment.
At any time during the cycle: Grade 2	Both cohorts: Hold treatment until improvement to grade 1. Maximize supportive care measures, e.g. ondansetron, lorazepam, dexamethasone, hydration. Continue with full dose of treatment.
At any time during the cycle: Grade 3	Hold treatment until recovered to grade 1. Maximize supportive care measures, e.g. ondansetron, lorazepam, dexamethasone, hydration. Cohort 1: Resume pevonedistat at next lower dose level once recovered. Cohort 2: Resume pevonedistat at next lower dose level once recovered. Administer pemetrexed at full dose 500mg/m^2. Reduce dose of cisplatin to 60 mg/m^2.

Dose Delays and Modifications for Peripheral Neuropathy or Ototoxicity (Cohort 2 only)

Neuropathy/Ototoxicity Grade	Modification instructions
Grade 1	Proceed with full-dose treatment of all agents.
Grade 2	Proceed with full-dose treatment of pevonedistat and pemetrexed. Reduce dose of cisplatin to 60 mg/m^2.
≥ Grade 3	Proceed with full-dose treatment of pevonedistat and pemetrexed. Discontinue cisplatin.

Dose Delays and Modifications for All Other Non-Hematologic Toxicities,

Toxicity Grade	Modification instructions
Grade 1 - 2	Proceed with full-dose treatment of all agents.
Grade 3	Hold treatment until recovery to grade 1 or 2. Cohort 1: Proceed with treatment with pevonedistat at next lower dose. Cohort 2: Proceed with treatment with pevonedistat at next lower dose. Lower pemetrexed to 400 mg/m^2 and cisplatin to 60 mg/m^2.
Grade 4	Hold treatment until recovery to grade 1 or 2. Resume treatment with dose reductions of all agents only at the discretion of the Principal Investigator.

Definition of dose limiting toxicity (Cohort 2 only)

All toxicity will be graded according to the National Cancer Institute (NCI) Common Toxicity Criteria, version 4.0. The grade of toxicity should be that seen despite maximal medical management. Attempts will be made as best as possible to determine whether the toxicity is related to pemetrexed, cisplatin, pevonedistat, or the combination.

Hematologic dose-limiting toxicity is defined as any:

- Grade 4 neutropenia lasting more than 7 consecutive days
- Grade 3 neutropenia with fever and/or infection where fever is 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
- Platelet count <10,000/mm^3 at any time

Non-Hematologic dose-limiting toxicity is defined as:

- 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 patients baseline values):
    - Of more than 4 weeks due to nonhematologic toxicities.
- Grade 3 or greater PT or aPTT elevation in the absence of anticoagulation
- 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 treatment. 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 use of optimal analgesia
- Patients experiencing concomitantLFT (≥3xULN) and bilirubin (≥2xULN) elevations without cholestasis and in absence of potential alternative cause (per Hy's Law)
- Other pevonedistat-related non-hematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require a dose reeducation or discontinuation of therapy with pevonedistat.
- Any other grade 3 or greater non-hematologic toxicity deemed at least possibly related to therapy by the investigator with the following exceptions:
    - Brief (<1 week) grade 3 fatigue
    - Grade 3 hypophosphatemia

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 cycle of therapy for treatment-related toxicities.

Dosing Modifications for Nonhematologic Toxicities

Pevonedistat Dose Adjustment Based on Serum Transaminases and Total Bilirubin

It is anticipated that LFTs (AST, ALT, and occasionally bilirubin) may be elevated for approximately 48 hours following the end of pevonedistat infusion on Cycle 1 Day 1.

For elevated LFTs of Grade 2 or 3 that occur on or after Cycle 1 Day 3, 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, pevonedistat dose may be resumed. For pevonedistat, a minimum of 1 full calendar day between any 2 doses should be maintained, and a maximum of 3 doses of pevonedistat within the cycle must not be exceeded.

For elevated LFTs of Grade 4 that occur on or after Cycle 1 Day 3, the 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 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, pevonedistat may be re-escalated.

Dosing Guidelines for 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.

Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Table Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	May be used judiciously but should not exceed a dose of 2 g in 24 hours.
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/μL while on study treatment. The dosing of hydroxyurea and changes to dosing of hydroxyurea must be recorded.
Clinically significant metabolic enzyme inducers	Excluded
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 pevonedistat dose until 72 hours before the next pevonedistat dose. For example, if a patient receives 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 pevonedistat, including but not limited to androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate]	

BCRP=breast cancer resistance protein, CYP=cytochrome P450,

Permitted Concomitant Medications and Procedures

Table 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

Table Concomitant Medications and Procedures Permitted During the Study

Therapy	Comment
	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/µL) 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/µL in the absence of clinical bleeding); see Section 6.9
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.

Precautions and Restrictions

Pregnancy

It is not known what effects pevonedistat has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Nonsterilized female patients of reproductive age group and male patients should use highly effective methods of contraception (see Appendix) through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal (See Appendix) for at least 1 year before the Screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [e.g., calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception. Female and male condoms should not be used together.)

- Female patients must agree to not donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

Male patients, even if surgically sterilized (i.ee, status post vasectomy), must agree to 1 of the following:

- Practice highly effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug, or

- Practice true abstinence, 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. Female and male condoms should not be used together.)

Male patients must agree to not donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

The Modified Response Evaluation Criteria in Solid Tumors Group (Modified RECIST) criteria will be used to evaluate the response to treatment.[23]

Target Lesions:

Change in disease will be assessed by measuring the tumor thickness perpendicular to the chest wall or mediastinum in up to three involved areas of pleural rind at least 2 cm apart on computed tomography scan, at baseline, and every other cycle (at least one measurement must be >1.5 cm).

Complete Response (CR): Complete absence of all signs of disease without any new lesions or disease-related symptoms.

Partial Response (PR): A reduction of at least 30%.

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

Progressive Disease (PD): An increase of 20% over the nadir measurement is defined as progressive disease.

Non-Target Lesions

All other lesions (or sites of disease) not included in the "target lesions," including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm with spiral CT scan) and truly non-measurable lesions, should be identified as non-target lesions and recorded at baseline. Measurements are not required and these lesions should be followed as defined below.

Lesions that are considered non-measurable include bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, abdominal masses that are not confirmed and followed by imaging techniques, and cystic lesions.

Complete response: Disappearance of all non-target lesions.

Non-complete response/Non-progression: Persistence of one or more non-target lesion.

Progression: Appearance of one or more new lesions. Unequivocal progression of existing non-target lesions.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started).In general, the patient'sbest response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

Conditions that may define early death include patients that have died without documentation of disease progression and before it was time to conduct the first tumor reassessment. Inevaluable patients have received protocol treatment and did not have any follow-up assessment completed before initiation of alternative treatment.

In some circumstances, it may be difficult to distinguish residual disease fromnormal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

Guidelines for Evaluation of Measurable Disease

All patients in this study will be getting a CT scan to include the target lesion.

Confirmation Measurement/Duration of Response

The duration of overall response is measured from the time measurement criteria are met for CR/PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

Duration of stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

13.1 CRITERIA FOR REMOVAL FROM STUDY

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(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
- Inability of subject to comply with study requirements

For patients who stop the treatment before 4 cycles, every effort will be made to have a CT scan at 18 weeks after treatment start, so that they can be have a standard evaluation of the primary objective. If a CT scan evaluation is not available, patients will not be replaced and they will be considered as not having clinical benefit.

14.0 BIOSTATISTICS

The primary objective of this study is to investigate pevonedistat as a single agent and in combination with chemotherapy in patients with MM with the use of two separate cohorts that will enroll patients concurrently. Cohort 1 will determine the efficacy of single agent pevonedistat in patients with previously treated MM and possess NF2 mutation; cohort 2 will examine the safety of pevonedistat in combination with pemetrexed/cisplatin in patients with previously untreated MM to establish the recommended phase II dose.

Cohort 1: Efficacy cohort

We chose clinical benefit rate (CBR = CR + PR + SD) at 18 weeks post initiation of treatment as the primary endpoint for this cohort based on the preclinical data showing growth inhibition with pevonedistat. We base the sample size calculation on the estimated 20%

clinical benefit as a benchmark, which we derive from the placebo arm of a phase III trial, and our own institutional data.[2,24] We consider an increase to 40% CBR as promising. A two-stage Simon's minimax design will be employed to the test the hypothesis that the true CBR is ≤20% versus the alternative hypothesis that the true CBR is at least 40% with type I and II error of 0.05 and 0.2, respectively. In the first stage, we will accrue 18 patients. If 4 or fewer show clinical benefit, then subject enrollment will be terminated and study declared negative. If at least 5 patients show clinical benefit in the first stage, we will request permission from the sponsor to enroll an additional 15 patients in the second stage. At the end of the study, if ≥11 patients out of total of 33 enrolled patients show clinical benefit, then further investigation of pevonedistat will be considered worthwhile. The study enrollment of the 19th patient will be suspended until the determination of the first-stage results, unless the benchmark of 5 patients with clinical benefit is achieved by then. All patients will be included in the primary analysis of clinical benefit, even if there are major protocol deviations. Patients are considered non-responses (no clinical benefit) if they are not evaluable (including if CT scan evaluation not available) or died during the study. If patients terminate treatment prior to 6 cycles, every effort will be made to have a CT scan at 18 weeks post treatment initiation so that they can contribute to the primary analysis. This study requires accrual of a minimum of 18 patients and up to a maximum of 33 patients if the cohort is expanded to the second stage. The accrual time is estimated to be between 10-24 months at the rate of 2 patients/month and a likely planned 4 months suspension between the first and second stages.

The CBR is defined as the proportion of patients CR, PR or SD at 18 weeks based on RECIST criteria. The CBR and corresponding exact 95% CI will be reported. Progression-free survival will be measured from the start of treatment until the documentation of disease progression or death due to any cause, whichever occurs first, and censored on the date of last tumor assessment document absence of tumor progression for patients who are still alive prior to data cutoff, dropout, or the initiation of alternate anticancer treatment. Overall survival will be determined as the time from the start of pevonedistat treatment to death, and censored on the last follow-up date. PFS and OS will be evaluated using the Kaplan-Meier method.[25] A sensitivity analysis will also be conducted for PFS and OS where early dropout patients will be considered as events.

All recorded toxicity data and adverse events of pevonedistat will be listed and tabulated by system organ class, preferred term and treatment. Any significant vital signs and clinical laboratory test results will be listed and summarized. Any significant physical examination findings and clinical laboratory results will be listed.

As a secondary objective, we explore downstream mechanistic biomarkers of pevonedistat activity such NEDD8-Cullin4 adduct, phosphorylated YAP and TAZ from on treatment core biopsies. These biomarkers will be measured by western blot, and qPCR. These methods have been previously reported in the literature {Hansen Cell Res 2015}; however, the data on reproducibility, repeatability have not been established. In this study, we will perform reproducibility testing (3 sites from the obtained biopsy specimen) and repeatability testing (perform test 3 times) of each assay to determine the coefficient of variation of each test. If the coefficient of variation is less than 15%, we will move forward in testing these correlative

biomarkers in a randomized phase II trial. Using histogramplots, we will graph the biomarker distribution of the assays performed on on-treatment biopsies.

Cohort 2: Safety cohort

In this 3-by-3 dose escalation design, we investigate the maximum tolerated dose (MTD) of pevonedistat in combination with the full dose of pemetrexed/cisplatin. Pevonedistat will be administered at the dose levels of 50%, 75% and 100% of the recommended single agent dose (see section 9.0). If none of the initial cohort of 3 has a dose-limited toxicity (DLT, as defined in Section 11.0), the dose level will be escalated. If one has a DLT that dose level will be expanded with 3 more patients. Dose escalation will stop if ≥2 DLTs are seen at a dose level. The MTD is defined as the highest dose level at which no more than 1 of the 6 patients at that level has a DLT. If no patient in the 3-patient cohort has a DLT and the dose level is under final consideration of the MTD, an additional three patients will be treated at that level for confirmation. Three dose levels plus a "-1" dose level are planned for this study. The maximum sample size is 24 patients for this dose escalation design. The probability of escalation is as follows:

True DLT rate	5%	10%	15%	20%	25%	30%	40%	50%
Probability of escalation	0.97	0.91	0.81	0.71	0.60	0.49	0.31	0.17

Adverse events will be graded according to the CTCAE version 4.0, with patients being assess weekly while on the treatment. Proportion of clinical benefit (CR+PR+SD) and response (CR+PR) will be summarized among patients treated at MTD.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Inclusion/Exclusion Criteria. Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures. During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist. The individual signing the Eligibility Checklist is confirming whether or not the participant is eligible to enroll in the study. Study staff are responsible for ensuring that all institutional requirements necessary to enroll a participant to the study have been completed. See related Clinical Research Policy and Procedure #401 (Protocol Participant Registration).

15.3 Randomization

Not applicable

16.1 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA will include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team. The data collected for this study will be entered into a secure database (Medidata). Source documentation will be available to support the computerized patient record. The principal investigator will maintain ultimate responsibility for the clinical trial.

16.2 Quality Assurance

Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluation and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the principal investigator for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.3 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center’s Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.4 Regulatory Documentation

Prior to implementing this protocol at MSK, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSK Institutional Review Board/Privacy Board (IRB/PB). There will be one protocol document..

The site that is conducting specimen analysis must submit the following documents to MSK before specimens can be shipped to the site:

- Participating Site 1572
- Conflict of Interest forms for Participating Site Investigators on the 1572

The site conducting data/specimen analysis should submit this protocol to its IRB according to local guidelines. Copies of any site IRB correspondence should be forwarded to MSK.

17.1 PROTECTION OF HUMAN SUBJECTS

Human Subjects Involvement, Characteristics, and Design

This project involves the treatment of human subjects with pevonedistat on a phase I/II protocol.

The subject population will include patients, age 18 or over, with advanced malignant pleural or peritoneal mesothelioma. Patients must have a Karnofsky Performance Status ≥70%. Other inclusion and exclusion criteria is specified at the beginning of this document to ensure enrollment of patients with adequate hematologic and biochemical function, and no other serious medical conditions. Patients who are pregnant or lactating are excluded, and all patients must use appropriate methods of contraception. About 42 patients will be enrolled.

Vulnerable populations will not be included in the research.

This study will be conducted only at MSKCC.

Sources of Materials

The data collected from patients on the study will include demographics, medical history, medication records, toxicities, radiologic responses, and outcomes such as time to progression and survival.

Archived tissue samples as well as fresh biopsy samples will be collected for correlative studies to elucidate the mechanism of drug action.

The data collected for this study will be entered into a secure database (Medidata) at Memorial Sloan Kettering Cancer Center. Source documentation will be available to support the computerized patient record.

The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

Potential Risks of Pevonedistat

There are potential risks in the pevonedistat program that require monitoring. While these toxicities may be severe or life threatening, it is anticipated that they can be managedby clinical monitoring and intervention. Patients will be monitored for these potential toxicities and for unanticipated toxicities when they receive pevonedistatfor at least 30 days after their last dose.

For detailed information please consult the current IB.

Adequacy of Protection Against Risks

Recruitment and Informed Consent: Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at MSKCC. If the investigator is a member of the treatment team, s/he will screen their patient's medical records and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

Subject participation is voluntary. The proposed study does not include patients under 18 years old. All patients will be required to sign a statement of informed consent that conforms to IRB guidelines. Informed consent will be documented by the use of a written consent form which has been approved by the IRB. Before protocol specified procedures are carried out, a study investigator or their staff explains the full details of the protocol and study procedures, as well as the risks involved to patients prior to their inclusion in the trial. Patients will also be informed that they are free to withdraw from the study at any time. The patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks and discomforts. This consent is obtained in the clinic by one of the physician investigators whose name is indicated on the face page of the protocol. All patients must read, discuss with consenting physician, and sign an IRB approved consent form indicating their consent to participate. This consent form conforms to the applicable requirements of 21 CFR 50.25 elements of informed consent. Written consent will be obtained by either the principal investigator, co-principal investigators, or participating investigators. The original signed consent forms will become part of the patient's medical record. Each patient will receive a copy of the signed consent form. There is absolutely no waiver of the consent. Consent must be documented in the medical record of each patient.

Protections Against Risk: Procedures for protecting against and minimizing risks to treatment and other clinical interventions is described within the text of the protocol. This includes toxicity monitoring, dose modification guidelines, and indications for removing patients from the study.

Potential Benefits of the Proposed Research to Human Subjects and Others

The potential benefits of the research to the subjects are not known and there may be no benefit to the research subject. Administration of pevonedistat will potentially cause disease regression. The potential benefits of the research to others are not known, but may include development of new therapies.

The risks to subjects are reasonable in relation to the anticipated benefits to the subjects and others based on the preclinical and clinical data derived on the study drug to date.

Importance of the Knowledge to be Gained

The treatment of MM is an important unmet need that could impact thousands of potential patients. This approach would also provide a proof of concept for targeting this pathway in other patients with tumors resulting from NF2 loss.

The risks to subjects are reasonable in relation to the anticipated benefits to the subjects and others given the broad potential of this therapy for NF2 related malignancies and the impact on possible future therapies.

17.2 Privacy

MSK's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.3 Serious Adverse Event (SAE) Reporting

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

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- 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.

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 'Reporting of Serious Adverse Events', the SAE report must be sent to the IRB within 5 calendar days of the event. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

Regardless of expectedness or causality, all SAEs must also be reported in English to Millennium Pharmacovigilance or designee:

> **Fatal and Life Threatening SAEs** within 24 hours of the sponsor-investigator's observation or awareness of the event
>
> **All other serious (non-fatal/non life threatening) events** within 4 calendar days of the sponsor-investigator's observation or awareness of the event

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject's condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

Follow-up information on the SAE may be requested by Millennium Pharmacovigilance (or designee).

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

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

US and Canada

Toll-Free Fax #: 1-800-963-6290

E-mail: TakedaOncoCases@cognizant.com **All other countries (Rest of World)**

Fax #: 1-202-315-3560

E-mail: TakedaOncoCases@cognizant.com

17.2.1 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug. The sponsor-investigator must fax a completed Pregnancy Form to the Millennium Pharmacovigilance or designee immediately (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Millennium Pharmacovigilance or designee will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study and MSKCC is notified, the sponsor-investigator will provide the external sponsor the information for their further action via faxing a completed Pregnancy Form to the Millennium Pharmacovigilance or designee (see Section 8.2). MSKCC will not be involved in the consent or data oversight of that pregnant individual.

Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Millennium (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints, call

Phone 1-844-ONC-TKDA (1-844-662-8532)

Email: GlobalOncologyMedinfo@takeda.com

Fax: 1-800-881-6092, Hours Mon-Fri, 9 a.m.- 7 p.m. ET

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

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCES

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20.0 APPENDICES

Lab Manual.