CLINICAL STUDY PROTOCOL

UMCC 2017.063

Phase II Trial of Pevonedistat (TAK-924) plus Docetaxel in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer

Indication: Relapsed Non-Small Cell Lung Cancer
Phase: II

Protocol History

Original	30 Jan 2017
Revision 1	22 Mar 2017
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Revision 3	16 May 2017
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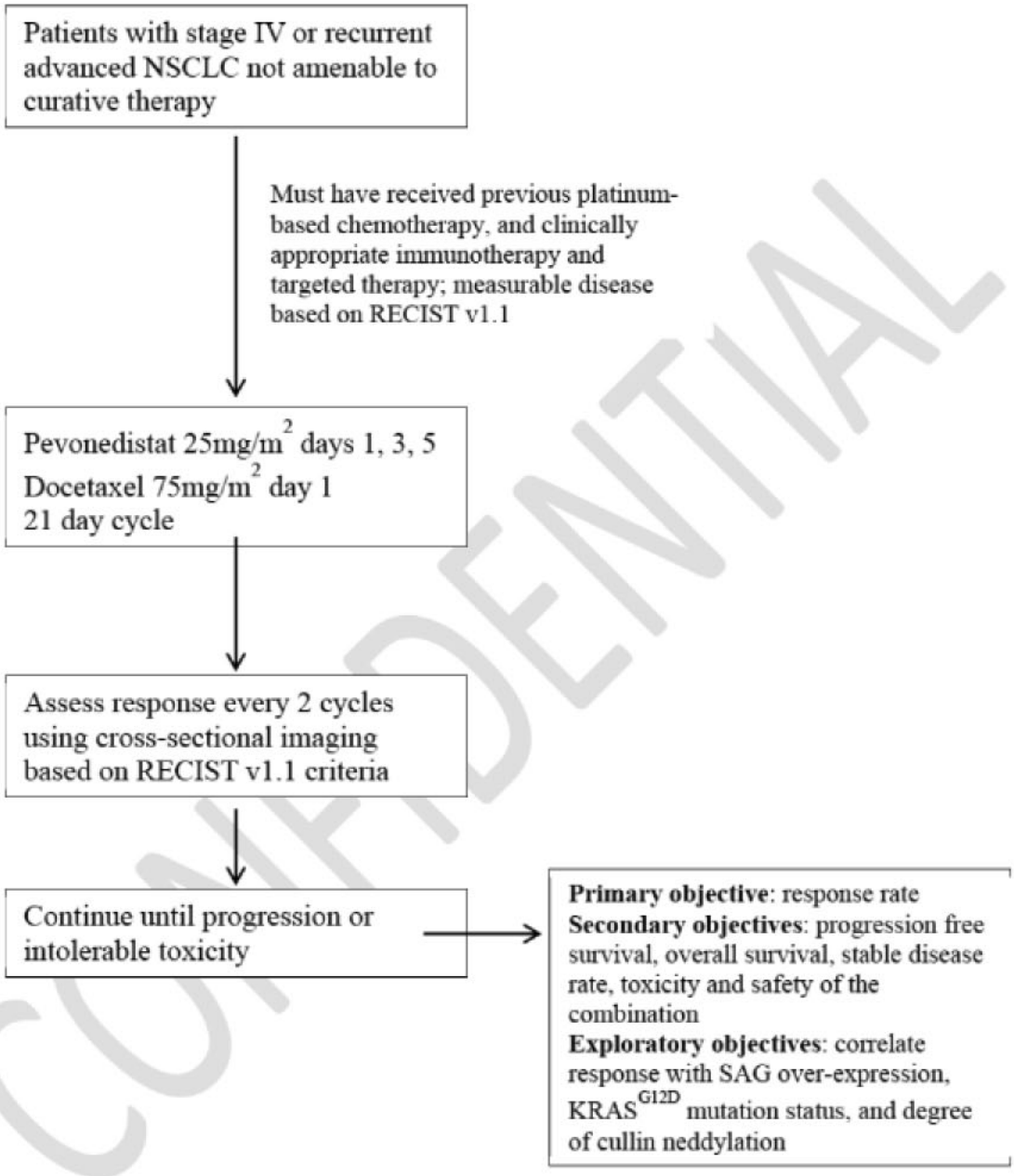
This is an investigator-initiated study. The principal investigator, Gregory Kalemkerian, (who may also be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

STUDY SYNOPSIS

Title	Phase II Trial of Pevonedistat (TAK-924) plus Docetaxel in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer
Phase	II
Methodology	Simon two-stage design
Study Duration	24 months
Study Center(s)	University of Michigan
Objectives	Primary • To determine the response rate with the combination of pevonedistat plus docetaxel in patients with relapsed or refractory non-small cell lung cancer (NSCLC). Response rate will be defined as complete response + partial response (CR+PR) Secondary • To determine the median progression-free survival and overall survival of patients treated with pevonedistat plus docetaxel and compare to historical controls treated with docetaxel alone • To determine the stable disease rate of patients treated with pevonedistat plus docetaxel • To determine the toxicity of pevonedistat plus docetaxel in patients with relapsed NSCLC Exploratory • Correlate response with SAG over-expression, $KRAS^{G12D}$ mutation status, and degree of cullin neddylation
Number of Subjects	Total = 37 (stage 1 = 17; stage 2 = 20)

Key Inclusion Criteria	• Stage IV NSCLC or recurrent NSCLC that is not amenable to curative therapy • Presence of measurable disease • Prior treatment with platinum-based chemotherapy, and clinically appropriate targeted therapy and immunotherapy • ECOG performance status 0-2 • Adequate organ function defined as AST and ALT $\leq$ 2.5 $\times$ ULN, bilirubin $\leq$ ULN, and creatinine clearance $\geq$ 50 ml/min • Adequate hematologic parameters
Key Exclusion Criteria	• Presence of significant comorbidities precluding participation in a clinical study • ECOG PS 3-4 • Prior treatment with docetaxel for non-small cell lung cancer • Pregnancy or lactation
Study Product(s), Dose, Route, Regimen	Docetaxel, IV, 75 mg/m^2 on day 1 of 21 day cycle Pevonedistat, IV, 25 mg/m^2 on days 1, 3 & 5 of 21 day cycle
Duration of Administration	Until progression or intolerable toxicity
Reference Therapy	Historical controls treated with single-agent docetaxel 75mg/m^2 IV on day 1 of a 21 day cycle
Statistical Methodology	This study is a single institution Phase II single arm trial to assess the efficacy of the combination of pevonedistat plus docetaxel in patients with previously treated advanced NSCLC. The primary endpoint is response rate which will be determined by RECIST v1.1 criteria using cross-sectional imaging. To minimize the number of patients to be treated, this study will utilize a Simon two-stage design, with interim analysis.

STUDY OVERVIEW DIAGRAM



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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AML	acute myelogenous leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
βhCG	beta-human chorionic gonadotropin
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CR	complete response
CRL	cullin-RING ligases
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P_{450}
DDI	drug-drug interaction
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
FDA	United States Food and Drug Administration
FSH	follicle stimulating hormone
G-CSF	granulocyte colony stimulating factor
GLP	Good Laboratory Practices
GM-CSF	granulocyte macrophage-colony stimulating factor
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
IRB	institutional review board
IV	intravenous; intravenously
KRAS G12D	KRAS mutation causing constitutive KRAS activation

Abbreviation	Term
LFT	liver function test(s)
MDS	myelodysplastic syndrome
MI	myocardial infarction
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NEDD8	neural precursor cell expressed, developmentally down-regulated 8
NSCLC	non-small cell lung cancer
PD	progressive disease (disease progression)
PK	pharmacokinetic(s)
PO	*per os*; by mou,h (orally)
PR	partial response
QD	*quaque die*; each day; once daily
QTc	rate-corrected QT interval (millisec) of electrocardiograph
RBC	red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SAG	Sensitive to Apoptosis Gene
SD	stable disease
TKI	tyrosine kinase inhibitor
ULN	upper limit of the normal range
US	United States

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Non-small cell lung cancer (NSCLC) is the leading cause of cancer-associated mortality worldwide. The prognosis for stage IV NSCLC remains dismal, with a 5-year survival rate of 1-2%. Beyond standard first-line platinum-based chemotherapy, other therapeutic options include tyrosine kinase inhibitors (TKIs) for patients with eligible mutations in the *EGFR*, *ALK*, *ROS1*, or *BRAF* genes, and immune checkpoint inhibitors, such as nivolumab, pembrolizumab, and atezolizumab. The immune checkpoint inhibitors have become standard second-line therapy after progression on chemotherapy. However, the response rate to these PD-1/PD-L1 inhibitors is only about 20% (1), leaving a significant number of patients who will be eligible for third-line therapy. Docetaxel, which was previously a standard second-line agent is now considered an appropriate third-line agent (2), with a response rate of only 9% (3, 4). There is therefore an unmet need for effective therapy in patients with recurrent NSCLC.

1.1.2 Study Drug

Pevonedistat (also known as TAK 924 and MLN4924) is a first-in-class, small molecule inhibitor of neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)-activating enzyme (NAE). The process of NEDD8 conjugation (neddylation) is catalyzed by E1 activating enzyme, E2 conjugating enzyme and E3 ligase. The major substrates of neddylation modification are cullin-RING ligases (CRLs), which are responsible for approximately 20% of all ubiquitylated proteins for targeted degradation. It is known that neddylation is required for CRL activity, which is over-activated in many human cancers, including NSCLC (5, 6). Pevonedistat belongs to the same drug category as bortezomib (also known as Velcade or PS-341), the first-in-class general proteasome inhibitor, approved by the U.S. Food and Drug Administration (FDA) for the treatment of relapsed/refractory multiple myeloma and mantle cell lymphoma (7). Given that bortezomib is a general inhibitor of proteasomes which inhibits the degradation of a wide array of cellular proteins, the drug toxicity is high which has limited its utility due to many associated side-effects (8). In contrast, by inhibiting cullin neddylation, pevonedistat selectively inhibits only CRL (9), with anticipated lesser toxicity. NAE, an E1 NEDD8 activating enzyme, is the first enzyme that catalyzes NEDD8 conjugation to CRL, a process required for their activity. CRL catalyzes the ubiquitylation and degradation of many substrate proteins with important roles

in cell cycle progression, signal transduction, DNA replication and repair, and tumor suppression (10-12). CRL activity is determined by the cullin-RBX complex, which catalyzes the transfer of ubiquitin to protein substrates. By complexing with distinct cullins, RBX family members (RBX1 and RBX2, also known as SAG) (13) constitute the catalytic core (12), which is activated by cullin neddylation. CRLs are activated in many human cancers by targeting degradation of tumor suppressor proteins thus promoting tumor cell growth, proliferation, and survival. As such, inhibitors of NAE activity are of potential therapeutic value in the treatment of various cancers by inhibiting CRL activity (5). Indeed, in the preclinical setting, pevonedistat has shown impressive anti-cancer activity in a variety of human cancer models (5).

1.1.3 Neddylation in NSCLC

Immunohistochemical staining of human lung adenocarcinomas and squamous cell carcinomas shows that elevated levels of global protein neddylation, relative to adjacent normal tissue, are associated with significantly worse overall survival (14). In a study using human and murine lung cancer models, Li *et al.* showed that pevonedistat specifically suppressed protein neddylation more effectively than bortezomib or MG132 (another proteasome inhibitor) with accumulation of CRL-E3 ligase specific substrates (14).

RBX2, also known as SAG (sensitive to apoptosis gene), was originally cloned in Dr. Yi Sun's lab at the University of Michigan (15). In a cell culture system, SAG over-expression inhibits apoptosis and promotes S-phase entry and cell growth (16). On the other hand, SAG knockout inhibits tumor cell growth and enhances apoptosis in human colon cancer cells (17). SAG is over-expressed in carcinomas of the colon, lung, stomach and liver, and is associated with poor prognosis in patients with NSCLC. In NSCLC samples, SAG over-expression was noted in 73% of adenocarcinomas and 67% of squamous carcinomas (18).

Through large-scale analysis of SAG mRNA expression in lung adenocarcinomas and its association with patient survival, the Sun laboratory found that SAG overexpression is correlated with decreased probability of survival and larger tumor burden. The same correlation was not seen with RBX1 expression (19). Through the inhibition of the NAE, pevonedistat also inactivates SAG-associated CRLs. The Sun laboratory has also shown that pevonedistat induces tumor shrinkage in a *KRAS*-induced murine lung adenocarcinoma model (19). While K*RAS* mutation and SAG overexpression are both required for tumorigenesis, *KRAS* mutation in the setting of SAG deletion led to a dramatic reduction of *KRAS*-induced lung tumor formation.

In summary, SAG overexpression is common in NSCLC and is associated with a poorer prognosis. Moreover, SAG inhibition induced by pevonedistat results in apoptosis in human NSCLC cells. However, clinical trials have not demonstrated significant responses with single-agent pevonedistat in patients with NSCLC, while the combination of pevonedistat plus cytotoxic agents does appear to induce clinical response. We therefore propose a phase II study to evaluate the activity of pevonedistat in combination with docetaxel in patients with previously treated, recurrent advanced NSCLC.

1.2 Preclinical Experience with Pevonedistat

Pevonedistat is a potent and selective inhibitor of NAE activity. 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 (9, 20, 21).

Pevonedistat demonstrated pharmacodynamic and antitumor activity in solid tumor, lymphoma, and acute myelogenous leukemia (AML) xenograft models when administered to immunocompromised mice by the subcutaneous route. 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 NSCLC xenograft model. Combination treatment with pevonedistat and carboplatin in both NCI-H69 human small cell lung cancer xenografts and LU1143 NSCLC xenografts resulted in significant antitumor activity.

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). Increased heart rate was observed at all doses, but in a separate GLP-compliant, 2-cycle, repeat-dose toxicology study in dogs, no 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. Pevonedistat did not result in lethality in either of the 5-cycle studies. The primary adverse effects in IV-dosed dogs included an acute phase response, 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 after a 2-week recovery period. Given that there were prominent effects on testes and ovaries in both dogs and rats, pevonedistat likely represents a substantial reproductive and developmental hazard. 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 (DDI) if pevonedistat is coadministered with drugs that are CYP3A inhibitors or inducers. The major elimination pathway of pevonedistat in animals is through the hepatic route. Detailed information regarding the nonclinical pharmacology and toxicology of pevonedistat is provided in the Investigator's Brochure (IB).

1.3 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 (22).
- Study C15002 in patients with lymphoma or multiple myeloma (23).
- Study C15003 in patients with AML, high-grade myelodysplastic syndrome (MDS), or acute lymphoblastic leukemia (ALL) (24).
- Study C15005 in patients with melanoma (25).

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, 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 data on 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 an 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 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 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 azacitidine 75 mg/m^2 (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28 day treatment cycle in elderly patients with treatment-naïve AML (26).

- Study C15010 (phase 1b) evaluated the MTD of pevonedistat plus docetaxel, gemcitabine, or the combination of carboplatin and paclitaxel, in patients with solid tumors (27, 28).

1.3.1 Pharmacokinetics

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 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 was generally moderate with 18% to 41% coefficient of variation (CV) for maximum concentration, 12% to 56% CV for area under the plasma concentration-time curve from time zero to 24 hours post-dose, 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's systemic clearance and volume 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. 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 [12-13]. 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 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.

For more detailed information on pevonedistat pharmacology please consult the current IB.

1.3.2 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.

For detailed information please consult the current IB.

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

1.3.3.1 Phase 1 Monotherapy Studies

Overall, 99 patients with advanced solid tumors or melanoma were treated with single-agent pevonedistat at doses ranging from 25 to 278 mg/m^2 in Study C15001 and Study C15005.

Common adverse events (AEs) (reported in ≥ 25% of patients in either study) were fatigue, nausea, anemia, decreased appetite, vomiting, diarrhea, myalgia, constipation, arthralgia, dizziness, and peripheral neuropathy. Dose-limiting toxicities (DLTs) included increased LFTs, increased creatinine, acute renal failure, acute hepatic failure, hypophosphatemia, and myocarditis. Acute renal failure occurred in 3 patients: 2 patients on Study C15001 at 196 mg/m^2 (1 patient also reported acute hepatic failure); and 1 patient on Study C15005 at 157 mg/m^2, who also had myocarditis and hyperbilirubinemia. Deaths on study that were considered related to study treatment included multi-organ failure (at 61 mg/m^2 QD × 5 consecutive days and 196 mg/m^2 in Study C15001), disease progression (at 83 mg/m^2 in Study C15001), and acute renal failure (at 209 mg/m^2 in Study C15005).

A total of 128 patients with hematologic malignancies (lymphoma, multiple myeloma, AML, MDS, or ALL) were treated with single-agent pevonedistat at doses ranging from 25 to 261 mg/m^2 in Study C15002 and Study C15003. Common AEs (reported in ≥ 25% of patients in either study) were increased ALT, anemia, increased AST, chills, constipation, decreased appetite, diarrhea, dizziness, dyspnea, fatigue, febrile neutropenia, headache, muscle spasms, myalgia, nausea, peripheral edema, pyrexia, and vomiting. DLTs included increased LFTs, febrile neutropenia, muscle spasms, thrombocytopenia, acute renal failure, orthostatic hypotension, cardiac failure, morbilliform rash, gastrointestinal necrosis, hypotension, lactic acidosis, and myocardial ischemia. Deaths on study that were considered related to study treatment (all in Study C15003) included 2 deaths from multi-organ failure (at 110 and 147 mg/m^2), 1 from sepsis (at 78 mg/m^2), and 1 from cardiopulmonary failure (at 45 mg/m^2).

While safety, PK, and pharmacodynamic objectives were the primary focus of these studies, disease response was also assessed. A total of 12 patients experienced a PR or better in the phase 1 monotherapy studies.

1.3.3.2 Phase 1 Combination Studies

Study C15010 is an ongoing phase 1b study evaluating the MTD of pevonedistat plus docetaxel, gemcitabine, or a combination of carboplatin and paclitaxel, in patients with solid tumors. As of 22 January 2016, enrollment has completed; 2 patients remain on study. The treatment arms are:

- Arm 1: pevonedistat on days 1, 3, and 5 with docetaxel 75 mg/m^2 on day 1 in a 21-day cycle.

- Arm 2 Lead-in: pevonedistat on days 1, 3, and 5 with carboplatin AUC 6 on day 1 in a 21-day cycle.

- Arm 2: pevonedistat on days 1, 3, and 5 with paclitaxel on day 1 and carboplatin on day 1 in a 21-day cycle. Per protocol, the dose levels for paclitaxel and carboplatin were to be based on the DLTs in the Arm 2 Lead-in cohort; because there were 2 DLTs in the Arm 2 Lead-in cohort doses were set at paclitaxel 175 mg/m^2 and carboplatin AUC 5.

- Arm 3: pevonedistat on days 1, 8, and 15 with gemcitabine 1000 mg/m^2 on days 1, 8, and 15 in a 28-day cycle.

Preliminary data are available for 64 patients enrolled who received at least 1 dose of pevonedistat in combination with standard therapy; these patients had completed a total of approximately 330 cycles, with medians ranging from 2 to 6 cycles of treatment across the 4 treatment groups. The starting dose levels for dose escalation and determination of pevonedistat MTD were 15 mg/m^2 for Arm 1 and Arm 2, and 25 mg/m^2 for Arm 3. Overall, the most common AEs (occurring in $\geq$ 25% of patients) were fatigue (56%), nausea (48%), anemia (41%), diarrhea (34%), constipation (31%), increased AST (31%), increased ALT (30%), and vomiting (28%).

Per the data cut off, 15 patients experienced Cycle 1 DLTs in Study C15010. Increased ALT or AST (or both) accounted for DLTs in 11 patients, febrile neutropenia was reported for 3 patients, and 1 patient experienced thrombocytopenia.

The MTD for Arm 1 was determined to be pevonedistat 25 mg/m^2 (on days 1, 3, and 5 with docetaxsel 75 mg/m^2 on day 1 in a 21 day cycle). No MTD was determined for the Arm 2 Lead-in per protocol, but these DLTs informed the dose selection for paclitaxel and carboplatin in Arm 2: paclitaxel 175 mg/m^2 and carboplatin AUC 5. The MTD for Arm 2 was determined to be pevonedistat 20 mg/m^2 (on days 1, 3, and 5 with paclitaxel 175 mg/m^2 and carboplatin AUC 5 on day 1 in a 21 day cycle). The gemcitabine combination arm (Arm 3) was closed to enrollment due to lack of tolerability (MTD was not determined).

A total of 26 (41%) patients experienced at least 1 serious AE (SAE). Febrile neutropenia was the only event reported for at least 1 patient in each of the treatment arms (reported for

2 of 26 patients in Arm 2 and 2 of 10 patients in Arm 3). Dyspnea was reported for 3 of the 22 patients in Arm 1 and for 1 patient in Arm 3. Abdominal pain was reported for 1 patient each in Arm 1 and Arm 3, and pneumonia was reported for 2 patients in Arm 1; all other events were reported for only 1 patient across the treatment arms. Fifteen patients discontinued the study because of treatment-emergent AEs. Events that resulted in study discontinuation that were assessed as at least possibly related to study drug treatment included increase in ALT and AST, serum bilirubin, and serum creatinine (1 patient each in Arm 1); thrombocytopenia, peripheral neuropathy, and neutropenia (1 patient each in Arm 2); leukopenia, lymphopenia, and pneumonitis (1 patient each in Arm 3), and febrile neutropenia (2 patients in Arm 3). Six on study deaths (within 30 days of the last dose of study drug) were reported with one death (Arm 3; due to febrile neutropenia) assessed as related to study treatment (pevonedistat plus gemcitabine). Twelve patients on Study C15010 achieved PR or better. Two patients in Arm 2 achieved a CR; 3 patients in Arm 1, 1 patient in the Arm 2 Lead in, and 6 patients in Arm 2 achieved a PR.

For more detailed information on pevonedistat's clinical safety and efficacy please consult the current IB.

1.4 Additional Safety Considerations

1.4.1 Increases in Liver Enzymes and Biochemical Tests

Grade 1 to Grade 4 increases in adverse events related to liver function analyses (such as for liver transaminases [up to Grade 4], bilirubin [up to Grade 3], and alkaline phosphatase [up to Grade 3]), have been noted in patients with advanced malignancies receiving pevonedistat as a single agent and in combination with standard of care cytotoxic therapies. All patients experiencing these increases in laboratory values have been asymptomatic. The elevations in laboratory values have been reversible with dose modification including dose delay and reduction.

1.4.2 Drug-Drug Interactions

Because the metabolic and excretion pathways of pevonedistat remain to be characterized in humans, the risk of DDIs between pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data. On the basis of preliminary findings, administration of pevonedistat with moderate CYP3A inhibitors is permitted, while use of strong CYP3A inhibitors or inducers should be avoided. As a general precaution, patients receiving concomitant medications, particularly those with narrow therapeutic indices, should be carefully monitored as the DDI potential between pevonedistat and other

drugs has not been formally studied in humans. Patients should also be instructed to consult with the investigator before taking any new medications, including over-the-counter products and herbal supplements.

2. STUDY OBJECTIVES

2.1 Primary Objective

The primary objective is to determine the response rate with the combination of pevonedistat plus docetaxel in patients with relapsed or refractory non-small cell lung cancer (NSCLC). Response rate will be defined as complete response + partial response (CR+PR)

2.2 Secondary Objectives

The secondary objectives include :

1. To determine the median progression-free survival and overall survival of patients treated with pevonedistat plus docetaxel and compare to historical controls with docetaxel alone

2. To determine the stable disease rate of patients treated with pevonedistat plus docetaxel

3. To determine the toxicity of pevonedistat plus docetaxel in patients with relapsed NSCLC

2.3 Exploratory Objectives

The exploratory objective is to correlate response with SAG over-expression, $KRAS^{G12D}$ mutation status, and degree of cullin neddylation.

3. STUDY ENDPOINTS

3.1 Primary Endpoints

1. Response rate (CR+PR) as measured by RECIST v1.1 criteria every 6 weeks until intolerable toxicity, patient withdrawal from study, or progression of disease

3.2 Secondary Endpoints

1. Median progression free survival as determined by date of enrollment to date of first documentation of disease progression per RECIST v1.1 criteria

2. Overall survival as determined by date of enrollment to date of death due to any cause; patients who are last known to be alive are censored at date of last contact

3. Stable disease rate as measured by RECIST v1.1 criteria

4. Frequency and severity of toxicities as measured by adverse events as defined by NCI CTCAE v4.03 throughout enrollment on trial

3.3 Exploratory Endpoints

Biomarker correlates: (1) SAG over-expression as determined by immunohistochemical testing (2) $KRAS^{G12D}$ mutation status as determined by sequencing and (3) degree of cullin neddylation as determined by Western blot, which can also be used to assess SAG overexpression. All of these assays will be performed on pre-treatment tumor samples. We will assess for correlation between these molecular changes and response to pevonedistat plus docetaxel, as well as with survival endpoints.

4. PATIENT ELIGIBILITY

4.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Patients 18 years of age or older

2. Histologically confirmed stage IV NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma, or not otherwise specified) or recurrent NSCLC not amenable to curative therapy

3. Patients must have demonstrated progression on or intolerance to platinum-based chemotherapy.

4. Patients whose tumors harbor an *EGFR* sensitizing mutation must have demonstrated progression on or intolerance to an FDA-approved first-line *EGFR* TKI; patients with the *EGFR* T790M mutation, must also have demonstrated progression on or intolerance to osimertinib.

5. Patients whose tumors harbor a *ROS1* rearrangement must have demonstrated progression on or intolerance to crizotinib.

6. Patients whose tumors harbor an *ALK* rearrangement must have demonstrated progression on or intolerance to an FDA-approved first-line TKI; if the first-line TKI was crizotinib, then they also must have demonstrated progression on or intolerance to an FDA-approved second-line TKI. Patients who received alectinib or ceritinib as first-line therapy and have demonstrated progression or intolerance will be eligible for this trial.

7. Patients whose tumors harbor the *BRAF* V600E mutation, must have demonstrated progression on or intolerance to the combination of dabrafenib and trametinib.

8. Patients whose tumors have PD-L1 expression in ≥50% of tumor cells must have demonstrated progression on or intolerance to pembrolizumab. Otherwise, patients who are eligible to receive an FDA-approved anti-PD-1/anti-PD-L1 agent as second-line therapy must also have demonstrated progression on or intolerance to the drug.

9. Eastern Cooperative Oncology Group (ECOG) performance status 0-2 (Appendix I)

10. Clinical laboratory values within the following parameters (repeat if more than 3 days before the first dose):

    a. Absolute neutrophil count (ANC) $\geq 1{,}500/mm^3$

    b. Platelet count $\geq 100{,}000/mm^3$

    c. Albumin > 2.7 g/dL

    d. 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.

    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN

    f. Creatinine clearance ≥ 50 mL/min

    g. Hemoglobin ≥ 8 g/dL. Patients may be transfused to achieve this value. Elevated indirect bilirubin due to post-transfusion hemolysis is allowed.

11. Female patients who are of childbearing potential and all males must agree to practice true abstinence or use effective methods of contraception (please see section

9.1.3 for additional information on pregnancy precautions and Appendix IV for the definition of post-menopausal)

12. Patients must be able to understand and sign the informed consent.

13. Patients must have measurable disease as defined by RECIST v1.1 criteria

14. It is prefereable that patients have an adequate tissue sample available for correlative studies evaluating SAG expression, cullin neddylation, and *KRAS*^{G12D} mutation, but lack of availability of such a tissue sample is not a requirement for trial enrollment.

4.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Treatment with any investigational products within 4 weeks before the first dose of any study drug

2. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of study procedures

3. Active uncontrolled infection or severe infectious disease, such as severe pneumonia, meningitis, or septicemia that require IV antibiotics within 2 weeks of starting study treatment

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

5. 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.

6. Life-threatening illness unrelated to cancer

7. Patients with uncontrolled coagulopathy or bleeding disorder

8. Known human immunodeficiency virus (HIV) seropositivity

9. Known hepatitis B surface antigen seropositivity 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.

10. Known hepatic cirrhosis or severe pre-existing hepatic impairment

11. Known cardiopulmonary disease defined as:

    - Unstable angina
    - Congestive heart failure (New York Heart Association Class III or IV; see Appendix II)
    - Myocardial infarction (MI) within 6 months prior to first dose of pevonedistat (patients who had ischemic heart disease resulting in MI and/or revascularization greater than 6 months before treatment and who are without cardiac symptoms may enroll)
    - Cardiomyopathy
    - Left ventricular ejection fraction < 50% as assessed by echocardiogram or radionuclide angiography
    - Clinically significant arrhythmia:
        1. History of polymorphic ventricular fibrillation or torsade de pointes
        2. Permanent atrial fibrillation [a fib], defined as continuous a fib for $\geq$ 6 months
        3. Persistent a fib, defined as sustained a fib lasting > 7 days and/or requiring cardioversion in the 4 weeks before screening
        4. Grade 3 a fib defined as symptomatic and incompletely controlled medically, or controlled with device (e.g. pacemaker), or ablation and

5. 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);
- Pulmonary hypertension

12. Uncontrolled high blood pressure (ie, systolic blood pressure > 180 mm Hg, diastolic blood pressure > 95 mm Hg)

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

14. Interstitial lung disease or pulmonary fibrosis

15. Systemic antineoplastic therapy or radiotherapy for other malignant conditions within 14 days before the first dose of any study drug, except for hydroxyurea.

16. Symptomatic or history of untreated brain or leptomeningeal metastases. Treated patients should be neurologically stable for 4 weeks after completion of appropriate therapy. Patients should be off steroids at least 3 days prior to start of therapy on clinical trial.

17. 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 (see Appendix III for more details).

18. Female patients who are lactating, breastfeeding, or have a positive pregnancy test

19. 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).

20. 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).

21. Known hypersensitivity to docetaxel or other drugs formulated with polysorbate 80

22. Prior therapy with docetaxel for non-small cell lung cancer

23. Peripheral neuropathy of CTCAE v4.03 grade ≥ 2

5. TREATMENT PLAN

5.1 Pre-treatment evaluation

1. Complete history and physical (including the date and site of diagnosis as well as the histology of NSCLC) should be completed within 2 weeks (14 days) of study entry. All previous treatments for NSCLC should be documented including the agents used, number of courses, best response to each regimen, and duration of response. For previous radiation therapy, the site radiated and the dose will also be documented.

2. Required laboratory testing: CBC with differential, serum total bilirubin, direct bilirubin, glucose, uric acid, alkaline phosphatase, AST, ALT, LDH, albumin, total protein, serum electrolytes (sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium), serum magnesium, serum phosphate, coagulation testing (INR, PT, PTT), and urinalysis are to be obtained within 14 days of study entry.

3. All radiological studies (including CT chest and any other relevant sites of disease) needed for tumor assessment should be performed within 28 days of study entry.

4. Brain imaging (CT head with contrast or MRI) must be obtained within 28 days of study entry.

5. Serum pregnancy test (for women of childbearing potential)

6. ECG

7. Pathology sample sent for SAG expression, cullin neddylation, and KRAS mutation (optional)

5.2 Drug administration

Pevonedistat will be administered at 25 mg/m^2 on days 1, 3 and 5 and docetaxel will be administered at 75 mg/m^2 on day 1 of a 21 day cycle per phase Ib data (28). On the days that both drugs are given together, docetaxel will be infused first, followed by pevonedistat.

To evaluate for toxicity, there will be a clinic visit prior to each cycle which will include history and physical exam as well as laboratory evaluation as outlined in the schedule of events (5.3). Tumor response will be evaluated every 2 cycles by RECISTv1.1 criteria using

cross-sectional imaging. Treatment will be continued until there is evidence of progressive disease, intolerable toxicity, or withdrawal from study per patient request

5.3 Schedule of Events

	Baseline[1]	Cycle 1					Cycle 2				Cycle 3 and beyond			End of Treatment[2]
		Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 8-21	Day 1	Day 3	Day 5	
Informed consent	X													
History and physical exam[3]	X	X					X				X			X
Vital signs	X	X[4]	X	X			X[4]	X	X		X[4]	X	X	X
Adverse event monitoring							X				X			
CBC with differential	X	X	X	X	X	X	X				X			X
Comprehensive metabolic panel[5]	X	X	X	X	X	X	X	X	X		X	X	X	X
Serum magnesium	X	X					X				X			X
Serum phosphate	X	X	X	X	X	X	X	X	X		X	X	X	X
Serum lactate dehydrogenase	X	X					X				X			X
Serum uric acid	X													X
Serum pregnancy test (for women of childbearing potential)	X													
Serum or urine pregnancy test (for women of childbearing potential)		X					X				X			
12-lead ECG[6]	X													X
Coagulation[7]	X													
Urinaylsis with microscopic analysis[8]	X													X
CT of chest and other relevant sites of disease[9]	X									X				
Brain imaging (CT head with contrast or MRI brain)	X													
Infusion of docetaxel		X					X				X			
Infusion of pevonedistat		X	X	X			X	X	X		X	X	X	

Pathology sample sent for SAG expression, cullinn neddylation, and *KRAS* mutation[9] (optional)	X													

1. Assessment for eligibility, including complete history and physical and required laboratory testing must occur within 14 days of starting therapy. Baseline cross sectional imaging (including brain imaging) must be obtained within 28 days of starting therapy. Except for hematology, procedures conducted during the screening period that are performed within 24 hours of cycle 1 day 1 can also be used as the baseline evaluation and do not need to be repeated. If dosing falls on a Monday, the collection window may be extended to collect samples on the previous Friday.
2. The end of treatment visit will occur 30 days (+10 days) after the last dose of pevonedistat or before the start of subsequent antineoplastic therapy if that occurs sooner. Patients will then be followed for overall survival. This will be done by a review of the medical chart if they remain at UMHS or through a telephone call every 3 months for a maximum of 5 years.
3. Includes evaluation of performance status.
4. If day 1 of the cycle falls on a Monday, but the patient was evaluated on the Friday prior, the weight from the Friday evaluation can be used to calculate study drug dosage. A new weight is not needed
5. The comprehensive metabolic panel consists of serum sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, calcium, glucose, total protein, albumin, total bilirubin, direct bilirubin, aspartate aminotransferase, alanine aminotransferase, and alkaline phosphatase
6. As clinically indicated during treatment
7. Coagulation includes PT, aPTT, and INR
8. 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
9. CT to asses response will be obtained every 2 cycles
10. SAG overexpression, cullin neddylation, and presence of $KRAS^{G12D}$ mutation not required for enrollment onto trial

5.4 Dose-Modification Guidelines

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 (NCI CTCAE).

Docetaxel modification guidelines:

Dose Level	Docetaxel Dose
0	75 mg/m^2
-1	60 mg/m^2
-2	50 mg/m^2

Pevonedistat modification guidelines:

Dose Level	Pevonedistat Dose
0	25 mg/m^2
-1	20 mg/m^2
-2	15 mg/m^2

5.4.1 Dose Modifications for Hematologic Toxicities

It is not anticipated that pevonedistat dose modifications would be necessary due to myelosuppression. However, if clinically indicated in the opinion of the investigator, the pevonedistat dose may be reduced one dose level. The pevonedistat dose may be re-escalated at the next cycle, if the toxicity has recovered to ≤ grade 1 or the patient's baseline.

On day 1 of all cycles patients should have neutrophil count $\geq 1.5 \times 10^9$/L and platelet count $\geq 100{,}000 \times 10^9$/L

The following dose modifications will be made for neutropenia and are for docetaxel only:

Nadir neutrophil count	Dose level
$>0.5 \times 10^9$/L	0
$\leq 0.5 \times 10^9$/L	-1

If the neutrophil nadir is $\leq 0.5 \times 10^9$/L at dose level –1, then the dose will be reduced to level –2. If the neutrophil nadir is $\leq 0.5 \times 10^9$/L at dose level –2 the patient can be continued at dose level –2 if the neutrophil count by first day of the next cycle is $\geq 1.5 \times 10^9$/L. Patients developing febrile neutropenia (one reading of oral temperature > 38.5°C or three readings

of oral temperature > 38.0°C in a 24-hour period) at dose level –2 will discontinue protocol therapy.

The following dose modifications will be made for thrombocytopenia and are for docetaxel only:

Nadir platelet count	Dose level
$> 25 \times 10^9$/L	0
$\leq 25 \times 10^9$/L	-1

If the platelet nadir count is $\leq 25 \times 10^9$/L at dose level –1, then the dose will be reduced to level –2. If the platelet nadir count is $\leq 25 \times 10^9$/L at dose level –2 the patient can be continued at dose level –2 if the platelet count by first day of the next cycle is $\geq 100{,}000 \times 10^9$/L.

5.4.2 Dose Modifications for All Non-hematologic Toxicities

Toxicity Grade	Modification Instructions
1-2	Proceed with full dose treatment for both drugs
3	Hold treatment until recovery to grade 1 or 2; proceed with treatment for both drugs at dose level -1
4	Hold treatment until recovery to grade 1 or 2; resumption of treatment with lower dose for both drugs at discretion of Principal Investigator

Pevonedistat Dose Adjustment Based on Serum Transminases 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 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.

A concomitant elevation in bilirubin ≥2×ULN AND transaminases (ALT and/or ALST) ≥3×ULN will lead to permanent discontinuation of the study drugs.

Pevonedistat Dose Adjustment Based on Hypophosphatemia

If hypophosphatemia is ≥ grade 3, pevonedistat 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.

Pevonedistat Dose Adjustment for Other Toxicities

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

5.4.3 Dose Modification of Peripheral Neuropathy Associated with Docetaxel

Grade	Docetaxel dose
0-1	no change
2	delay[1]
3-4	discontinue protocol therapy

[1]The patient will be delayed for a maximum of 2 weeks to allow the neuropathy to improve to ≤ grade 1, and then the patient will be restarted at the next lower dose level. If a patient develops grade 2 neuropathy at dose level –2, but recovers to ≤ grade 1 by day 1 of the next cycle, further therapy at dose level –2 may be continued.

5.5 Criteria for Retreatment and Dose Delays

5.5.1 Retreatment within a Cycle

If dosing of either drug is delayed for safety reasons, retreatment may be resumed upon resolution of the safety condition. For pevonedistat, a minimum of 1 full calendar day

between any 2 doses should be maintained. A maximum of 3 doses of pevonedistat should not be exceeded in any cycle.

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

5.5.2 Initiation of a New Cycle

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

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

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

For hematologic toxicity a delay in the initiation of a cycle by 4 weeks or greater because of lack of recovery from treatment-related hematologic toxicity (resolved to ≤ grade 1, to patient's baseline values, or to a level considered acceptable by the sponsor-investigator) will trigger a dose reduction if treatment resumes.

5.6 Number of Patients

Enrollment of patients will occur by the Simon two-stage design. We will first enroll 17 patients; if ≥ 2 responses are observed, then we will plan to accrue another 20 patients for a total of 37 patients. A patient will be considered enrolled once they are consented, screened, and eligibility has been verified.

5.7 Duration of Study

Patients will continue on study as long as repeat scans every 2 cycles (i.e. 6 weeks) are without evidence of progression and they are continuing to tolerate therapy without significant toxicity.

5.8 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the sponsor-investigator. The appropriate study personnel will maintain records of study drug receipt and dispensing.

5.9 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Unacceptable adverse events
- Protocol violation
- Lost to follow-up
- Progressive disease
- Intercurrent illness that prevents further administration of treatment
- Subsequent anti-cancer therapy
- Study termination

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. At the termination of the study, all patients will continue to be followed for survival either through a review of their medical records if they continue their care at UMHS or through a telephone call every 3 months for a maximum of 5 years.

6. STUDY PROCEDURES

6.1 Administration of Study Drugs

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

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

The amount of study drug to be administered will be based on body surface area (BSA). BSA will be calculated using a standard formula on Cycle 1 Day 1, and on Day 1 of subsequent cycles if the patient experiences a >5% change in body weight from the weight used for the most recent BSA calculation. If Day 1 of a cycle falls on a Monday, but the patient is being evaluated on the Friday before, the weight from the evaluation on Friday can be used to calculate the amount of study drug and a new weight is not needed.

6.2 Management of Clinical Events

6.2.1 Management of Extravasation

Based on nonclinical findings as detailed in the IB, pevonedistat is considered a nonvesicant drug. Although no published guidelines are available for extravasation of nonvesicants, the investigator is encouraged to follow institutional guidelines. Some general advice in case of extravasation includes immediately stopping drug infusion and elevating the affected limb to minimize swelling.

6.2.2 Management of Acute Hypersensitivity to Docetaxel

Severity of Symptoms	Treatment Guidelines
Mild symptoms: localized cutaneous reactions such as mild pruritus, flushing, rash	· consider decreasing the rate of infusion until recovery from symptoms, stay at bedside and monitor patient · then, complete docetaxel infusion at the initial planned rate
Moderate symptoms: any symptom that is not listed above (mild symptoms) or below (severe symptoms) such as generalized pruritus, flushing, rash, dyspnea, hypotension with systolic BP > 80 mm Hg	· interrupt docetaxel infusion · give diphenhydramine 50 mg IV with dexamethasone 10 mg IV; monitor patient until resolution of symptoms

	· resume docetaxel infusion after recovery of symptoms; depending on the physician's assessment of the patient, docetaxel infusion should be resumed at a slower rate, then increased incrementally to the initial planned rate, *(eg. Infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, then finally, resume at the 1-h infusion rate)* · depending on the intensity of the reaction observed, additional oral or IV premedication with an antihistamine should also be given for the **next cycle** of treatment, and the rate of infusion should be decreased initially and then increased back to the recommended 1-hour infusion, *(eg. infuse at an 8 hour rate for 5 minutes, then at a 4-h rate for 5 minutes, then at a 2-h rate for 5 minutes, and finally, administer at the 1-h infusion rate)*
Severe symptoms: any reaction such as bronchospasm, generalized urticaria, systolic BP ≤ 80mm Hg, angioedema	· immediately discontinue docetaxel infusion · give diphenhydramine 50 mg IV with or without dexamethasone 10 mg IV and/or epinephrine as needed; monitor patient until resolution of symptoms · Patient should come off protocol.

6.2.3 Guidance for Clinical Assessment and Management of Hemodynamic Compromise

Due to the underlying conditions of patients with advanced malignancies, patients must be carefully evaluated at screening and before each pevonedistat dose for early symptoms and signs of hemodynamic compromise and active infection. For those patients for whom there is a concern of dehydration, IV fluid repletion is strongly recommended. For all patients with anemia, and especially for patients with hemoglobin values ≤ 8 g/dL at screening or during the conduct of the study, RBC transfusions should be considered before pevonedistat dosing. Patients who experience signs and symptoms of hemodynamic compromise after pevonedistat dosing should be followed closely and managed with supportive care, including hospitalization as clinically indicated.

6.3 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited 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	
Known BCRP inhibitors (ie, 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.

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

6.4 Permitted Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

Therapy	Comment
Anti-platelet agents (eg, 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 (eg, G-CSF, GM-CSF)	In general, the use of myeloid growth factors is discouraged and should be restricted. 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.
Platelet transfusion	Permitted as medically necessary per institutional guidelines (e.g., for platelets <10,000/μL in the absence of clinical bleeding)
Red blood cell transfusion	To be considered for all patients with anemia, especially those with hemoglobin values ≤8 g/dL.

G-CSF=granulocyte colony-stimulating factor, GM-CSF=granulocyte macrophage colony-stimulating factor.

7. MEASUREMENT OF EFFECT

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee (29), including modifications as stated in RECIST v1.1 criteria (30).

7.1 Definitions

Evaluable for objective response: Only those patients who have measurable disease present at baseline, have received at least 2 cycle(s) of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable).

7.2 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (or MRI) for studies with a slice thickness of ≤5mm, or twice the slice thickness
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in subsequent scans only the short axis will be measured and followed.

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered may be defined in the protocol when appropriate.

Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), representative of all involved organs, and those that lend themselves to reproducible repeated measurements.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, sagital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20

mm x 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but <15 mm) should be considered non-target lesions. Nodes that have a short axis <10 mm are considered nonpathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions: All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare cases 'unequivocal progression' (more details to follow). In addition, it is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

7.3 Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and in subsequent scans. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and > 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

CT and MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

7.4 Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

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

Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level.

Incomplete Response/Stable Disease (SD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or 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). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires:**
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/SD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: 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.

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or 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).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: 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.

Progression-Free Survival

Progression-free survival is defined as the duration of time from start of treatment to time of progression.

8. ADVERSE EVENTS

8.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Serious Adverse Event (SAE)

An AE is considered "serious" if, in the view of the investigator it results in any of the following outcomes:

- Death: If death results from (progression of) the disease, the disease should be reported as the event (SAE).
- A life-threatening adverse event: An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it

occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important medical event: Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened during the course of the study, it should be reported as an SAE.

Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label)
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1.1 for the list of expected adverse events related to the drug under study

Unexpected Adverse Event

An AE is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, published medical literature, the protocol, or the informed consent document.

8.2 Adverse Event Reporting

An AE may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Data on AEs will be collected from the time of initial dose through 30 days after the last dose of pevonedistat. AEs which are **serious** must be reported to Takeda (or designee) from the first dose of pevonedistat up to and including 30 days after administration of the last dose of pevonedistat. Any SAE that occurs at any time after completion of pevonedistat treatment or after the designated 30-day follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Takeda(or designee). SAEs will continue to be followed until:

- Resolution or the symptoms or signs that constitute the SAE return to baseline;
- There is a satisfactory explanation other than the study regimen for the changes observed; or
- Death

Any medical condition or laboratory abnormality with an onset date before initial dose of pevonedistat is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

Since this is an investigator-initiated study, the principal investigator, Gregory Kalemkerian, MD, also referred to as the sponsor-investigator, is responsible for reporting SAEs to any regulatory agency and to the sponsor-investigator's IRB.

Regardless of expectedness or causality, all SAEs must also be reported in English to Takeda 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 investigator must report all events meeting the criteria and definition of a serious adverse that are unexpected and possibly related (definite, probable or possible) to pevonedistat to the local IRB within 7 days of study team's knowledge.

The SAE report must include at minimum:

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

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

Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Takeda, 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

Suggested reporting form:

- SAE Report Form (a sample will be provided)
- US FDA MedWatch 3500A:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

- Any other form deemed appropriate by the sponsor-investigator

8.3 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 Takeda or designee immediately (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Takeda 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, the sponsor-investigator must also immediately fax a completed Pregnancy Form to Takeda or designee (see Section 8.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

Suggested Pregnancy Reporting Form:

Pregnancy Report Form (a sample will be provided)

8.4 Adverse Event Characteristics

CTCAE Term

AE description and grade: The descriptions and grading scales found in the NCI CTCAE version 4.03 will be utilized for AE reporting. All appropriate treatment areas should have

access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be down loaded from the CTEP web site. https://evs.nci.nih.gov/ftp1/CTCAE/About.html

Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.

Definite – The AE *is clearly related* to the study

Probable – The AE *is likely related* to the study

Possible – The AE *may be related* to the study

Unlikely – The AE *is doubtfully related* to the study

Unrelated – The AE *is clearly NOT related* to the study

9. DRUG INFORMATION

9.1 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.

Pevonedistat is a cytotoxic anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling pevonedistat.

The specified number of 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 24 hours at 2°C to 8°C. After 24 hours of storage at 2°C to 8°C, the prepared IV bag must be used within 6 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

Pevonedistat (TAK-924/MLN4924) will be provided in 10-mL glass vials at a concentration of 10 mg/mL. 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 BSA. BSA will be calculated using a standard nomogram on Cycle 1, Day 1, 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, 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.

Full details are available in the IB.

9.1.1 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 managed by clinical monitoring and intervention. Patients will be monitored for these potential toxicities and for unanticipated toxicities when they receive pevonedistat for at least 30 days after their last dose.

9.1.1.1 Potential Risks from Phase 1 Studies

Events have been reported in completed phase 1 studies primarily at doses and schedules substantially higher than doses administered in the current study. These events are being considered potential risks for the doses and schedules in the current studies:

- Multi-organ failure that could result in death
- Renal failure
- Clinically significant cardiac arrhythmias.
- Myelosuppression with increased susceptibility to infection, bleeding, and anemia
- Acute phase response
- Gastrointestinal toxicity resulting in dehydration and/or electrolyte imbalance
- Hypophosphatemia
- Elevation of liver enzymes

9.1.1.2 Potential Risks Confounded by Underlying Disease or Malignancy

Events have been reported from clinical trials that are confounded by the patient's underlying medical condition, including malignancy. These events are noted in the absence of randomized, controlled data:

- Fatigue
- Chills
- Decreased appetite
- Neutropenia
- Febrile neutropenia
- Gastrointestinal bleeding

9.1.2 Cycle 1, Day 1 Toxicity/Multi Organ Failure

A comprehensive review of the clinical trial safety data has shown that C1D1 toxicity involving multi-organ failure, including SAEs of renal, hepatic, and cardiac failure, some with a fatal outcome, has been observed in phase 1, single agent pevonedistat studies at doses equal to or above 110 mg/m^2. Based on the observation that these events are associated with higher pevonedistat doses, Takeda determined that all newly enrolling patients would receive pevonedistat at doses equal to or below 100 mg/m^2.

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.

In October 2012, 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. As of January 2016, approximately 180 additional patients have been treated in single agent and combination studies, and no C1D1 SAEs 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/m^2 in combination with a CYP3A inhibitor.

9.1.3 Pregnancy Precautions

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 V) through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal (See Appendix IV) for at least 1 year before the Screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice one highly effective method and one additional effective (barrier) method of contraception (see Appendix V), 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 [eg, 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 (ie, status postvasectomy), 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 [eg, 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).

9.2 Docetaxel

Docetaxel is an anti-neoplastic agent belonging to the taxoid family. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-*tert*-butylester, 13-ester with 5-20-epoxy-1,2,4,7,10,13-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate.

Docetaxel is an anti-neoplastic agent that disrupts the microtubular network that is essential for mitotic and interphase cellular functions, resulting in the inhibition of mitosis.

Pharmacology

The area under the curve (AUC) was dose proportional following doses of 70-115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment pharmacokinetic model, with half-lives of 4 min, 36 min, and 11.1 hr, respectively. Mean values for total body clearance and steady state volume of distribution were 21 L/h/m^2 and 113 L, respectively. Docetaxel was eliminated in both the urine and feces, but fecal excretion was the main elimination route. The pharmacokinetics of docetaxel were not influenced by age or gender, and docetaxel total body clearance was not modified by pretreatment with dexamethasone. In patients with mild to moderate liver function impairment (AST and/or ALT > 1.5 times the ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). In vitro studies showed that docetaxel is about 94% protein bound. In vitro studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism can be inhibited by CYP3A4 inhibitors, such as

ketoconazole, erythromycin, troleandomycin, and nifedipine. CYP3A4 inhibitors and/or substrates may lead to substantial increases in docetaxel blood concentrations.

Human Toxicity

The dose-limiting toxicity at 75 mg/m^2 was severe neutropenia which occurred in 66% of patients. This is the FDA-approved dose in relapsed stage IV NSCLC, given every 21 days. Treatment-related mortality occurred in 2.8% of patients. Hypersensitivity reactions were observed in 5.6% of patients. Febrile neutropenia and severe infections were observed in 7% and 10%, respectively. Fluid retention of any sort occurred in 33% of patients with 2.8% experiencing severe fluid retention. Severe neurological side-effects were observed in almost 5% of patients. Significant gastrointestinal adverse effects, such as nausea and diarrhea, ranged from 2.8% to 5%. Other significant side-effects were asthenia in 18%, severe nail changes in 1.8%, and alopecia in 57%.

Docetaxel for this study will be from commercial stock. The preparation, reconstitution, storage, handling and dispensing of docetaxel will be per institutional standards.

Docetaxel for Injection Concentrate is supplied in a single-dose vial as a sterile, pyrogen-free, non-aqueous, viscous solution with an accompanying sterile, non-pyrogenic, diluent (13% ethanol in Water for Injection) vial.

10. BIOMARKERS

Based on our published pre-clinical data, we will assess SAG over-expression, *KRAS*^{G12D} mutation status, and degree of cullin neddylation in pre-treatment tumor samples and will correlate these results with response to pevonedistat plus docetaxel and with survival endpoints. SAG over-expression will be assessed by immunohistochemical staining on pre-treatment tumor samples with antibodies against SAG. *KRAS*^{G12D} mutation status will be assessed by sequencing of pre-treatment biopsy samples. Cullin neddylation will be determined by Western blot, which can also be used to assess SAG overexpression. The presence of these molecular changes will not be used as an eligibility criterion for study entry. All assays will be performed after enrollment onto the study.

Available tumor biopsies will be obtained from enrolled NSCLC patients and cut into half. The first half will be frozen for subsequent DNA isolation and sequencing analysis for potential Kras mutation, particularly *KRAS*^{G12D} mutations (direct biomarker). The second half of tumor tissues will be fixed in 10% formalin and embedded in paraffin. Five-µm-thick

sections will be cut for: a) H&E staining and microscopic examination for tumor classification; and b) immunohistochemistry staining, which will be performed using the ABC Vectastain kit (Vector Laboratories) with antibodies against SAG (direct biomarker), pIκBα (NFκB pathway, SAG substrate), p65 (NFκB pathway; Santa Cruz Biotechnology), pERK (MAPK pathway), and pS6K (mTORC pathway; Cell Signaling Technology Inc). Sections will be developed with DAB and counterstained with haematoxylin. Tissue samples with high SAG staining are expected to have reduced staining of pIκBα, p65 nuclear localization and enhanced staining of pERK and pS6K.

11. STATISTICAL AND QUANTITATIVE ANALYSES

11.1 Statistical Methods

The primary objective of the study is to determine the response rate of the combination of pevonedistat and docetaxel in patients with recurrent NSCLC after progression on platinum-based chemotherapy and immunotherapy. Response rate, defined as the sum of complete + partial response (CR+PR), as measured by RECIST v1.1 will be the primary statistical endpoint.

11.2 Determination of Sample Size

A two-stage optimal Simon design will be used to minimize the number of patients to be treated. Due to lack of reasonably effective treatments for this disease, we have purposely relaxed the Type 1 error probability to < 0.15, but limited the Type II error probability to <0.10. Assume that this combination will not be of further interest if the true response rate were less than 0.10 and assume that a true response rate of at least 0.25 would be of definite clinical interest. This phase II study design permits early termination of patient entry after the first 17 response-evaluable (r-e) patients have been accrued if there are no encouraging results. A maximum of 37 r-e patients will be studied unless undue toxicity or other medical reasons warrant early termination of patient entry. This will provide a 90% power to detect the drug as promising, if that is true. Both point and exact binomial confidence interval estimates of the RECIST response rate will be calculated.

Stopping Rules of the Two Stage Design

1. Accrue 17 r-e patients. If 1 or 0 responses are observed stop the study and conclude that this combination is not worthy of further evaluation.

2. If ≥ 2 responses are observed, accrue an additional 20 r-e patients (i.e. the second stage of patient accrual). If 5 or fewer responses are observed in the 37 r-e patients, we will conclude that the combination of pevonedistat and docetaxel does not have significant activity. If ≥ 6 responses are observed, we will conclude that this combination is potentially a viable treatment option for patients with advanced NSCLC.

The procedure described above tests the null hypothesis that the true response rate is < 0.10 vs. the alternative hypothesis that the true response rate is > 0.25. The Type 1 error (i.e. the probability of rejecting null hypothesis when it is true) is 0.144. The power (i.e. the probability of correctly concluding that the agent is active) of this procedure is 0.901 when the true response rate is 25%. The probability of early termination with this design is 0.482 when the true response rate is 10%.

Accrual is expected to be 2 patients per month which will provide completion of accrual to stage one in 9-10 months. Interim analysis will conclude after follow-up of 2 months. Second stage accrual will be completed in an additional 10-12 months. Total trial time will be approximately 24 months.

11.3 Populations for Analysis

Intent-to-Treat Population: All patients consented and enrolled in the trial.

Response Evaluable Population: Only those patients who have measurable disease present at baseline, have received at least 2 cycles of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 2 will also be considered evaluable.)

Safety Evaluable Population: Patients who receive any treatment on protocol will be considered evaluable for safety.

11.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be described for the response evaluable and safety evaluable populations using means with standard deviations and counts with proportions.

11.5 Efficacy Analysis

The primary efficacy analysis is response rate and will include the response count and proportion with the associated exact 85% binomial confidence interval in the response evaluable population. If stage 2 is initiated then the efficacy analysis methods will be as described by Koyama and Chen (31).

Secondary endpoints of efficacy include progression-free survival, overall survival and stable disease rate as measured by RECIST. Progression-free survival and overall survival will be analyzed using Kaplan-Meier methods. Kaplan-Meier plots and product-limit estimates for medians and associated confidence intervals will be reported. Stable disease rate will be reported as the count and proportion of patients who achieve stable disease with the associated exact binomial confidence interval.

Biomarker analysis will examine SAG expression as determined by immunohistochemical testing, $KRAS^{G12D}$ mutation status as determined by sequencing, and cullin neddylation as determined by Western blot, all performed on pre-treatment tumor samples. We will assess for correlation between these molecular changes and response to pevonedistat and docetaxel with frequencies and chi-square statistics. Association of the biomarkers with survival endpoints will be described using Kaplan-Meier methods.

11.6 Safety Analysis

All recorded toxicity data and adverse events will be listed and tabulated by system organ class. 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.

12. DATA AND SAFETY MONITORING

This trial will be monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan.

The study team will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/unanticipated problem reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular

meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Committee on a quarterly basis for independent review.

13. ADMINISTRATIVE REQUIREMENTS

Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda (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 Takeda 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 Takeda (refer to Section 8.2).

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15. APPENDICES

Appendix I: Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.(32)

Appendix II: New York Heart Association Classification of Cardiac Disease (33).

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

Appendix III: Excluded CYP3A Inducers

Use of strong CYP3A inducers listed in the table should be avoided during pevonedistat therapy. Note that HIV medications that are strong CYP3A inducers are not included in this list because HIV-positive patients are excluded from study participation.

Strong Inducers (≥80% decrease in AUC)
Carbamazepine
Phenytoin
Phenobarbital
Primidone
Rifabutin
Rifampin
Rifapentine
St. John's wort

Abbreviations: AUC=area under the plasma concentration versus time curve; CYP=cytochrome P450.
Please refer to the following sources for additional information:
medicine.iupui.edu/clinpharm/ddis/main-table/ and
fda.gov/drugs/developmentapprovalprocess/developmentresources/%20druginteractionslabeling/ucm093664.htm

Appendix IV: Definition of Postmenopausal

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However in the absence of 12 months of amenorrhea, a single FSH measurement is insufficient. Please refer to the following source for additional information:

European Heads of Medicines Agencies Clinical Trial Facilitation Group; hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_ CTFG_Contraception.pdf

Appendix V: Methods of Contraception Considered Effective

Acceptable Methods Considered to Highly Effective

Birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibitor of ovulation[1]:
  - Oral
  - Injectable
  - Implantable[2]
- Intrauterine device (IUD)[2]
- Bilateral tubal occlusion[2]
- Vasectomized partner[2,3]
- Sexual Abstinence[4]

Methods that are Considered Less Highly Effective

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[5]
- Cap, diaphragm or sponge with spermicide[5]

Source: European Heads of Medicines Agencies (HMA) Clinical Trial Facilitation Group (CTFG); see hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf

1) Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.
2) Contraception methods that in the context of this guidance are considered to have low user dependency.
3) Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the woman of childbearing potential participant of the study and that the vasectomised partner has received medical assessment of the surgical success.
4) In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

A combination of male condom with either cap, diaphragm or sponge with spermicide (double-barrier methods) are also considered acceptable, but not highly effective, birth control method

UNIVERSITY OF MICHIGAN
CONSENT TO BE PART OF A RESEARCH STUDY

INFORMATION ABOUT THIS FORM

You may be eligible to take part in a research study. This form gives you important information about the study. It describes the purpose of the study, and the risks and possible benefits of participating in the study.

Please take time to review this information carefully. After you have finished, you should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others (for example, your friends, family, or other doctors) about your participation in this study. If you decide to take part in the study, you will be asked to sign this form. Before you sign this form, be sure you understand what the study is about, including the risks and possible benefits to you.

1. GENERAL INFORMATION ABOUT THIS STUDY AND THE RESEARCHERS

Study title:
Phase II Trial of Pevonedistat (TAK-924) plus Docetaxel in Patients with Previously Treated Advanced Non-Small Cell Lung Cancer (UMCC 2017.063)

Company or agency sponsoring the study:
The University of Michigan is the sponsor of this trial and Dr. Gregory Kalemkerian is the lead investigator. The study is partially funded by Takeda (maker of pevonedistat) and internal University of Michigan funding.

Names, degrees, and affiliations of the principal investigator and study coordinator (if applicable):
Principal Investigator
Gregory Kalemkerian, MD University of Michigan, Internal Medicine – Hematology/Oncology

1.1 Key Study Information

You may be eligible to take part in a research study. This form contains important information that will help you decide whether to join the study. Take the time to carefully review this information. You should talk to the researchers about the study and ask them any questions you have. You may also wish to talk to others such as your family, friends, or other doctors about joining this study. If you decide to join the study, you will be asked to sign this form before you can start study-related activities. Before you do, be sure you understand what the research study is about.

A research study is different from the regular medical care you receive from your doctor. Research studies hope to make discoveries and learn new information about diseases and how to treat them. You should consider the reasons why you might want to join a research study or why it is not the best decision for you at this time.

Research studies do not always offer the possibility of treating your disease or condition. Research studies also have different kinds of risks and risk levels, depending on the type of the study. You may also need to think about other requirements for being in the study. For example, some studies require you to travel to scheduled visits at the study site in Ann Arbor or elsewhere. This may require you to arrange travel, change work schedules, find child care, or make other plans. In your decision to participate in this study, consider all of these matters carefully.

This is a Phase II study, which means the goal is to test the safety and effectiveness of the investigational study drug, in other words - does it work against your type of cancer, and do the benefits outweigh the risks and side effects. This is usually done by comparing the outcomes of subjects in the study to those of people who previously

received standard treatment. This study is examining the use of pevonedistat and docetaxel to see if it will help in preventing the cancer from coming back. Your protected health information and biospecimens (including blood, urine and optional tissue) will be collected for this research study. More information will be provided later in this document.

There can be risks associated with joining any research study. The type of risk may impact whether you decide to join the study. For this study, some of these risks may include serious health complications that may be life threatening, requiring hospitalization or prolonging hospitalization, or new symptoms from the use of the study drug pevonedistat in combination with docetaxel. For risk information specific to pevonedistat and/or docetaxel refer to Section 5.1 of this consent form. More detailed information will be provided later in this document.

This study may offer some benefit to you now or others in the future. There is a possibility that your cancer may respond favorably to the investigational study drug, improvement in the quality of your life, and/or prolonged life. Your participation in this study may benefit patients in the future with this disease. More information will be provided later in this document.

You may continue to receive the study drug as long as your cancer is not getting worse and you do not have any significant side effects. We estimate the amount of time you will participate in the study could be up to a year. Your doctor will follow your condition every 3 months for up to 5 years after you finish the study drug.

You can decide not to be in this study. Alternatives to joining this study include: other available treatments such as immunotherapy or targeted therapy, one chemotherapy agent (docetaxel or pemetrexed alone), participation on another research study with a different study drug (if available), or receive supportive care for your disease without an anti-cancer treatment.

Even if you decide to join the study now, you are free to leave at any time if you change your mind.

More information about this study continues in Section 2 of this document.

2. PURPOSE OF THIS STUDY

2.1 Study purpose:

This is a Phase II single arm study to test the safety and effectiveness of the combination of pevonedistat plus docetaxel in subjects with previously treated advanced non-small cell lung cancer (NSCLC).

Pevonedistat is an investigational drug, which means it is not approved by the Food and Drug Administration (FDA).

Docetaxel has been FDA approved as monotherapy for the treatment of locally advanced or metastatic non-small cell lung cancer.

3. INFORMATION ABOUT STUDY PARTICIPANTS (SUBJECTS)

Taking part in this study is completely **voluntary**. You do not have to participate if you don't want to. You may also leave the study at any time. If you leave the study before it is finished, there will be no penalty to you, and you will not lose any benefits to which you are otherwise entitled.

3.1 Who can take part in this study?

You are being asked to take part in this study because you have confirmed Stage IV NSCLC or recurrent NSCLC and have previously received platinum-based chemotherapy.

Every study has strict guidelines for determining which people may participate. These are called eligibility criteria. You will need to meet all of these criteria before you can participate in this study. If you agree to consider participating in this study, you will undergo evaluations to see if you meet the eligibility criteria for this study. Even though you may meet all the criteria for participation, it is possible that you may not be enrolled in this study for other reasons. Eligibility criteria for this study include:

- You must be over 18 years of age
- You must not be pregnant, breast-feeding or are trying to get pregnant
- You must not have had prior treatment with docetaxel for non-small cell lung cancer

There are many other eligibility requirements which will be discussed with you during the screening phase of the study.

3.2 How many people (subjects) are expected to take part in this study?
Approximately 37 subjects are expected to participate in this study, all at the University of Michigan.

4. INFORMATION ABOUT STUDY PARTICIPATION

4.1 What will happen to me in this study?
The study team will explain the research study and answer any questions you have about the study. If you still want to participate in the study the study team will request you sign the consent form prior to any activities occurring that pertain to the study. Once your consent is obtained, the study team will look through your medical chart, ask you questions, and begin scheduling tests and procedures to determine if you are eligible for the study. The study team will inform you of the types of tests and procedures required before the study begins.

Once it is determined you are eligible to enter the study, tests and procedures done at your study visits as part of your regular cancer care will continue, but some may be done more often because you are participating in this research study. Also, some of the tests or procedures may have to be repeated if, for example, they were done too long ago or the results are not normal.

Some tests and procedures may be done that are not part of your regular cancer care and are being done only for this research study. Tests and procedures that are performed more often or are not part of your standard cancer care will be identified below as "Research".

During the study you must:

- follow the instructions you are given
- come to the study center for your visits with the study doctor
- tell the study doctor or study staff about any changes in your health and/or medications you are taking
- tell the study doctor or study staff if you want to stop being in the study at any time

Acetaminophen and acetaminophen-containing products may be used but should not exceed a dose of 2g in 24 hours.

Before starting the study:
You will need to have the following exams, tests or procedures to find out if you can be in this study. If you have had some of them recently, they may not need to be repeated.

- You will be asked about your medical history including any past treatments, surgeries, infection, and autoimmune diseases.
- You will be asked about any medications you are taking, including any over the counter medicines, vitamins or herbal treatments.
- You will have a physical exam including measurement of your height, weight, blood pressure, heart rate, respiratory rate and temperature.
- You will have blood tests (for routine complete blood counts, chemistry, and coagulation; some of these are for RESEARCH) and urine tests (RESEARCH) to check your health. The total amount of blood needed is about 15ml, or 3 teaspoons.
- Brain imaging (CT with contrast or MRI) must be obtained within 28 days of registration.
- You will have blood tests to check for pregnancy if you are a woman able to have children.
- Electrocardiogram (ECG) will be done to check the electrical activity of your heart (RESEARCH).
    - Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity.
- Computed tomography (CT) of the chest and other relevant sites of disease will be done to assess the extent of your cancer. MRI is acceptable for body scans.
    - A CT scan uses special x-ray equipment to make detailed pictures of body tissues and organs. For the CT scan, you may be given a "contrast material" (a special dye that makes it easier for doctors to see different tissues in your body). You will be asked to lie still and may be asked to hold your breath for a few seconds. The CT scan is done in the Radiology Department and takes about half an hour.
- OPTIONAL: If there is enough tissue sample available from your biopsy for research studies it will be used to look at several biomarkers. Your tissue sample will be stored at Dr. Yi Sun's lab at the University of Michigan for the duration of the study until after biomarker studies are performed. Any remaining tissue will be returned back to the University of Michigan Pathology Department or outside institution that provided it. The resulting information will be stored as part of your record in the study but will not be permanently stored as part of the permanent health record. You may withdraw your specimen and any resulting information at any time. You will not be told the results of the analysis. Your specimens will not be shared. No one will receive any financial benefit from research on your tissue sample. You will be able to make your choice in Section 12 (RESEARCH).

Study Intervention:

Pevonedistat:

Pevonedistat will be given through a vein in your arm (via IV) on days 1, 3, and 5 of each 21-day cycle (RESEARCH).

Docetaxel:

Docetaxel will be given through a vein in your arm (via IV) on day 1 of each 21-day cycle.

Procedures:

Day 1 of each cycle:

- You will have a physical exam including measurement of your height, weight, blood pressure, heart rate, respiratory rate and temperature.
- You will be asked about any side effects or illness you experience.
- You will have blood tests (totaling about 10ml or 2 teaspoons) for routine complete blood counts and chemistry tests to check your health; some of these are for RESEARCH.
- You will receive pevonedistat and docetaxel via IV.
- You will have urine or blood tests to check for pregnancy if you are a woman able to have children.

Days 3 and 5 of each cycle:

- You will have your blood pressure, heart rate, respiratory rate and temperature measured.
- You will receive pevonedistat via IV.
- You will have blood tests for routine complete blood counts and chemistry tests to check your health; some of these are for RESEARCH.

Days 8 and 15 of Cycle 1 only:

- You will have blood tests for routine complete blood counts and chemistry tests to check your health; some of these are for RESEARCH. The total amount of blood will total about 10ml or 2 teaspoons.

Every two (2) cycles, which is six (6) weeks, you will have a CT scan to assess the response of your cancer.

You will receive study drugs until your cancer progresses, you have intolerable side effects, or you decide to withdraw from the study.

End of Treatment

Approximately thirty days after your last dose of pevonedistat or before you start subsequent anticancer therapy, you will have the following procedures:

- Physical exam including measurement of your height, weight, blood pressure, heart rate, respiratory rate and temperature.
- Electrocardiogram (ECG) will be done to check the electrical activity of your heart (RESEARCH).
    - Wires or "leads" will be attached to your chest with an adhesive and you will be asked to lie still while the machine prints out an electrical "record" of your heart activity.

- You will be asked about any side effects or illness you experience.
- Blood tests (for routine complete blood counts, chemistry, and coagulation; some of these are for RESEARCH) and urine tests (RESEARCH) to check your health.

Follow-up

Once you have completed the study, you will be followed through review of your medical chart if you remain at the University of Michigan. Otherwise, we will be contacting you by telephone every 3 months for a maximum of 5 years to ask about your health.

4.2 How much of my time will be needed to take part in this study?

The length of your study visits will vary depending on which procedures need to be done. The screening visit may take approximately 4 hours.

On Day 1 of each cycle you will receive both pevonedistat and docetaxel. These visits may take approximately 3 hours. On days when you receive pevonedistat only, these visits may take approximately 2 hours. All other visits will take approximately 2 hours.

4.3 When will my participation in the study be over?

You will receive study drugs until your cancer progresses, you have intolerable side effects, or you decide to withdraw from the study. From enrollment, your study participation is expected to last about 9 months.

4.4 What will happen with my information and/or biospecimens used in this study?

Your collected information and biospecimens may be shared with Takeda.

Your collected information and biospecimens may also be shared with other researchers, both here or around the world, or with companies. Any sharing is subject to contractual obligations with the Sponsor. Additionally:
• With appropriate permissions, your identifiable collected information and biospecimens may be shared, and/or,
• Without your additional consent, your identifiable private information and identifiable biospecimens may be stripped of identifiers and used for future research studies or distributed to another researcher for future research studies.

5. INFORMATION ABOUT RISKS AND BENEFITS

5.1 What risks will I face by taking part in the study? What will the researchers do to protect me against these risks?

Your study doctor and study staff will monitor you closely for side effects. Even with frequent blood tests and other examinations, taking the study drug involves risks, and some side effects cannot be predicted. Side effects can range from mild to severe and life-threatening. Many side effects will get better when you stop taking the study drug, but some may be long lasting or may never go away. Side effects may even cause death. You should tell your study doctor immediately about any side effects that you have or any change in how you feel while on this study. If you have side effects, your dose may have to be reduced, or you may have to stop taking the drugs and wait until you feel better before you start again. Your study team may give you medicines or lower your dose of drugs to help lessen side effects. If any side effect is intolerable, you may have to permanently stop taking the drugs.

We will minimize the risks by monitoring you carefully. We will provide the usual supportive care that would be routinely given to someone with your condition. If you have side effects from the investigational study treatment, we will make appropriate adjustments as defined by the study protocol. You may need to discontinue the investigational study treatment if the side effects are too serious. If you have signs of infection, you will receive appropriate antibiotics. If you have signs of bleeding you may need to receive transfusions of platelets, plasma, or red cells. If you are at risk of having blood clots, you will receive an anticoagulant (blood thinner). If your hemoglobin level is too low, you may receive a red cell transfusion. If you start feeling sick to your stomach, you will be given medications to help reduce nausea. If you have vomiting, you may be given fluids through an IV.

Risks Associated with Pevonedistat and Docetaxel

The following are risks associated with receiving the combination of pevonedistat and docetaxel:

Very Common (more than 1 user in 10)

- feeling tired (fatigue)
- feeling sick to your stomach (nausea)
- low red blood cell count (anemia)
- loose watery stools (diarrhea)
- increased liver enzymes (AST, ALT) which can cause liver damage
- fever (pyrexia)
- feeling short of breath (dyspnea)
- decrease in white blood cell count that can increase risk for infection (neutropenia)
- pain in your abdomen
- low blood levels of an electrolyte called potassium, which can cause an irregular heart beat (hypokalemia)
- vomiting
- muscle pain (myalgia) and joint pain (arthralgia)

Common (1 to 10 users in 100)

- low platelets, which may cause bleeding and bruising (thrombocytopenia)

- difficulty falling or staying asleep (insomnia)
- low blood pressure (hypotension)
- dehydration
- change in taste (dysgeusia)
- flushing
- weakness, numbness and pain, usually in your hands and feet (peripheral neuropathy)
- headache
- fluid retention, usually in lower limbs (peripheral edema)
- low blood levels of an electrolyte called magnesium, which can cause weakness and muscle cramping (hypomagnesemia)
- low blood levels of an electrolyte called sodium (hyponatremia)
- constipation
- loss of appetite

Uncommon (1 to 10 users in 1,000)

- low platelets, which may cause bleeding and bruising (thrombocytopenia)
- dizziness
- urinary tract infection
- feeling weak and having no energy (asthenia)

Rare (1 to 10 users in 10,000)

- fever with dangerously low white blood cell count (febrile neutropenia)
- death (two patients died in a previous study, but it was due to progression of their disease and not because of the chemotherapy they received)
- severe pneumonia
- infection causing severe widespread inflammation requiring hospitalization, sometimes in the intensive care unit (septic shock)
- significant changes in the electrical activity in your heart (ST depression, electrocardiogram)

Risks Associated with Pevonedistat

The following risks are associated with receiving pevonedistat as a single agent. These are in addition to what is already listed above for the combination.

Very Common (more than 1 user in 10)

- cough
- elevated heart rate
- single- or multi-organ failure (severe problems with the liver, kidneys, and/or heart) that could cause death. This occurred at doses and schedules that are no longer being used.
- chills
- low blood levels of phosphate – possible bone damage (hypophosphatemia)

Common (1 to 10 users in 100)

- pain in your back
- increase of creatinine in the blood, a substance normally eliminated by the kidneys into the urine. This may mean that your kidneys are not functioning properly.
- increase of bilirubin in the blood, a substance normally processed by the liver. This may mean that your liver is not functioning properly (hyperbilirubinemia).

- decrease of albumin in your blood, which can lead to swelling in the extremities (hypoalbuminemia)
- low blood levels of calcium – possible weakness and/or cramping (hypocalcemia)

Uncommon (1 to 10 users in 1,000)

- anxiety
- feeling confused
- pain with urination (dysuria)
- elevated blood sugars (hyperglycemia)
- increased sweating (hyperhidrosis)
- stuffy nose (nasal congestion)
- throat pain
- accumulation of fluid in your lung that can make you more short of breath (pleural effusion)
- skin rash
- ulcers in your mouth (stomatitis)
- wheezing

Rare (1 to 10 users in 10,000)

- A reaction called an acute phase response where you may have a fever, high white blood cell count, and a change in certain protein levels in your body. This will be checked on blood work that is done during the study.

Risks Associated with Docetaxel

During the study you will receive an anti-cancer drug called docetaxel (Taxotere™). This drug is approved by the FDA in the United States for the treatment of NSCLC cancer. Like many other anti-cancer chemotherapy drugs, docetaxel can cause side effects and some can be serious.

The following risks are associated with receiving docetaxel as a single agent for NSCLC. These are in addition to what is already listed above for the combination and for single agent pevonedistat.

Very Common (more than 1 user in 10)

- hair loss (alopecia)

Common (1 to 10 users in 100)

- issue with nails (nail disorder)
- allergic reaction (hypersensitivity)

Rare (1 to 10 users in 10,000)

- blisters
- very severe blistering skin disease (Stevens-Johnson Syndrome)
- very severe blistering skin condition leading to loss of a large portion of your skin (toxic epidermal necrolysis)
- redness, swelling, and pain on the palms of the hands and/or soles of the feet (hand and foot syndrome)
- permanent hair loss (permanent alopecia)
- hepatitis
- seizures
- sudden brief loss of consciousness (transient loss of consciousness)
- brief visual disturbances; flashes, flashing lights, partial loss of vision or blindspot

- hearing loss (ototoxicity)
- death (treatment related)

Receiving the combination of pevonedistat and docetaxel may lead to you receiving lower or inadequate doses of docetaxel than what is currently FDA approved because of toxicities associated with the experimental drug pevonedistat.

If you do not understand what any of these risks mean, please ask the study doctor or study staff to explain these terms to you.

Other Risks You Should Consider

Electrocardiogram (ECG)
An ECG shows the electrical activity of the heart by placing several small adhesive pads that re attached to wires on your chest and limbs (called leads) and connecting them to a machine that reads the signal. There may be minor discomfort, similar to removing a bandage, when the electrodes taped to your chest are removed.

Blood Draws
Collection of blood samples may cause pain, bleeding, bruising or infection. It is also possible that you may feel lightheaded or faint. Please tell your study doctor or the study nurse if you do not feel well after having your blood drawn at any time during your study participation.

CT Risk
The contrast substance injected during the CT scan may cause pain, burning feeling, sweating and rarely an allergic reaction that can be serious. If you know you're allergic to iodine; you must inform your doctor immediately. The contrast agent used in the CT scan may cause kidney damage, especially if you're diabetic, dehydrated and if you're older. In addition, your thyroid function may be affected. CT imaging uses ionizing radiation, which increases your risk of cancer. Everyone is exposed to naturally occurring ionizing radiation every day. The amount of radiation exposure from 1 CT scan is approximately comparable to 1-3 years of natural background radiation.

MRI RISK
An MRI scan uses a magnetic field and radio waves to create images of the organs and tissues within your body. MRIs done for research that use IV contrast have risks similar to MRIs done for clinical care. Contrast is used to improve the pictures of the inside of the body made by the MRI. Common risks of MRI include: feeling fearful of being in a small enclosed space (claustrophobia) when you are lying inside the MRI scanner, feeling uncomfortable because of the loud noises made by the machines, and feeling uncomfortable with the physical sensations you may feel during the process. You are also exposed to some risk because of the injected contrast, gadolinium-DTPA, which may cause headache, nausea, and local burning sensation.

The contrast agent, gadolinium has been linked to development of Nephrogenic Fibrosing Dermopathy (NFD), also known as Nephrogenic Systemic Fibrosis (NSF). NFD is a thickening of the skin, organs and other tissues and is a rare complication in subjects with kidney disease who undergo an MRI with contrast material. To help prevent this, we will check how well your kidneys work before you have any MRIs. Because of the use of contrast, all female subjects who are able to have children will be required to use adequate birth control. If you have implanted metal objects such as a pacemaker, artificial limbs, or metal joints, you will not be able to have an MRI done, and may not be able to take part in this research.

Reproductive Risks

Because pevonedistat has only been tested in animal and early human studies, it is unknown whether pevonedistat can affect a male patient's ability to produce sperm, and for women, permanently stop the ovaries from producing eggs. The study medication may be a risk to an unborn child or breast-feeding baby. For future childbearing you should consider banking sperm or eggs, prior to administration of pevonedistat.

Although the effect of pevonedistat on fetus or unborn child has not been studied in humans, results from an animal study showed that pevonedistat at higher doses caused fetal harm. There was no fetal harm at lower doses of pevonedistat. Based on this information and knowledge of how this drug works, it is likely to be harmful to embryo or fetus.

Women

If there is ANY chance that you can get pregnant, you must either agree to not have vaginal intercourse or you must use TWO types of birth control (one from each list below) AT THE SAME TIME. These birth control methods must be used from the time of enrollment, all during treatment including during temporary breaks from therapy, and for at least 4 months after discontinuation of the study regimen. The following methods are considered acceptable birth control methods:

Primary forms

- tubal sterilization (tubes tied)
- partner's vasectomy
- intrauterine device
- hormonal contraceptives - (includes transdermal patch, injectables, implantables)

Secondary forms

- male latex condom with or without spermicide
- diaphragm with spermicide
- cervical cap with spermicide
- vaginal sponge (contains spermicide)

Any birth control method can fail. The reports of birth control failing are more frequent for female patients who use only a single form of birth control. Using two forms of birth control at the same time greatly reduces the chances of pregnancy.

In addition, women should not donate eggs (ova) while taking part in the study and for at least 4 months after the discontinuation of the study regimen. Any pregnancy will be followed until its final outcome.

Men

Men must agree to either abstain from sexual activities that could result in pregnancy or use an acceptable form of birth control while taking part in the study and for at least 4 months after the discontinuation of the study regimen. Acceptable forms of birth control are male latex condom (with or without spermicide) or vasectomy. In addition, men should not donate sperm or semen while taking part in the study and for at least 4 months after the discontinuation of the study regimen.

Tell your study doctor or study staff right away if your partner becomes pregnant. If your partner becomes pregnant while you are enrolled in this clinical trial, your partner will be asked to provide information about the pregnancy outcome. Your partner will be asked to sign a separate Pregnant Partner consent form before this information is collected related to both herself as well as the baby. The Institutional Review Board / Ethics Committee (IRB/EC), a group that oversees subject safety, will be told about the pregnancy.

As with any research study, there may be additional risks that are unknown or unexpected.

Genetic Information Nondiscrimination Act (GINA)

The federal Genetic Information Nondiscrimination Act (GINA) generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. This law does not protect you against genetic discrimination by companies that sell life insurance, disability insurance, or long-term care insurance. Under this law:

- Health insurance companies and group health plans may not request your genetic information that we obtain from this research
- Health insurance companies and group health plans may not use your genetic information when making decisions regarding your eligibility or premiums
- Employers with 15 or more employees may not use your genetic information that we obtain from this research when making a decision to hire, promote, or fire you or when setting the terms of your employment

GINA does not apply to the following groups, however these groups have policies in place that provide similar protections against discrimination:

- Members of the US Military receiving care through Tricare
- Veterans receiving care through the Veteran's Administration (VA)
- The Indian Health Service
- Federal employees receiving care through the Federal Employees Health Benefits Plans

5.2 What happens if I get hurt, become sick, or have other problems as a result of this research?
The researchers have taken steps to minimize the risks of this study. Even so, you may still have problems or side effects, even when the researchers are careful to avoid them. Please tell the researchers listed in Section 10 about any injuries, side effects, or other problems that you have during this study. You should also tell your regular doctors.

If you think you have an injury or illness that is related to your participation in this clinical trial, it is important that you tell your study doctor immediately. If you have a clinical trial related injury or accident, the study staff will make sure that you get medical treatment.

You will receive appropriate medical care for any side affects you have while participating in this study. Your study doctor may also lower the drug dose or stop drug if you experience side effects.

You must inform your study doctor immediately if there are any changes in your health/condition, or if you have any concerns regarding the study. If for any reason you are seen by another healthcare provider or admitted to another hospital, you should make known your participation in this research study. These healthcare providers may wish to contact your study doctor to discuss your condition. Your study doctor may need to contact your other doctors if you develop any potentially significant, unexpected diseases or conditions that may have been caused by the study intervention or procedures or are discovered during the study.

5.3 If I take part in this study, can I also participate in other studies?
Being in more than one research study at the same time, or even at different times, may increase the risks to you. It may also affect the results of the studies. You should not take part in more than one study without approval from the researchers involved in each study.

5.4 How could I benefit if I take part in this study? How could others benefit?
You may not receive any personal benefits from being in this study. There is a chance that the study intervention may improve your quality of life or increase the length of disease-free survival by controlling the growth of the cancer. The researchers also hope that the information learned from this study will help other patients with this type of cancer in the future.

5.5 Will the researchers tell me if they learn of new information that could change my willingness to stay in this study?
Yes, the researchers will tell you if they learn of important new information that may change your willingness to stay in this study. If new information is provided to you after you have joined the study, it is possible that you may be asked to sign a new consent form that includes the new information.

6. OTHER OPTIONS

6.1 If I decide not to take part in this study, what other options do I have?
You do not have to participate in this trial to receive care for your cancer. There may me other ways of treating your cancer. These include:

- You may receive other available treatments for your cancer, which may include immunotherapy (drugs that stimulate your immune system to fight the cancer) or pills that target a specific mutation that your cancer may have. You will discuss this with your doctor to determine if any of these treatments are appropriate for you.
- You may receive one chemotherapy agent, such as docetaxel or pemetrexed alone, instead of the combination of drugs (docetaxel + pevonedistat) used in this study
- You may be eligible for other cancer research studies
- You may receive treatment for pain or other symptoms only
- You may receive no treatment at all

Please talk to your doctor about your choices before you decide if you will take part in this study.

7. ENDING THE STUDY

7.1 If I want to stop participating in the study, what should I do?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. You will not lose any benefits to which you may otherwise be entitled. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell one of the persons listed in Section 10 "Contact Information" (below).

You are free to partially or completely end your participation in the study. An example of partially ending your participation would be to discontinue receiving study intervention, while still allowing continuation of study follow-up procedures.

Please note that any information collected before you withdraw will be kept and used to complete the research.

Please note that even if you withdraw consent for further follow-up or contacts, if the study doctor becomes aware of additional safety information this will be reported to the sponsor in order to comply with legal or regulatory requirements.

7.2 Could there be any harm to me if I decide to leave the study before it is finished?
You are free to leave the study at any time. If you leave the study before it is finished, there will be no penalty to you. This will not affect your future medical care in any way and you will not lose any benefits to which you may otherwise be entitled. Tell the study doctor if you are thinking about stopping or decide to stop. It is important to tell the study doctor if you are thinking about stopping so any risks can be evaluated by your doctor. He or she will also tell you how to stop safely and discuss what follow-up care and testing could be most helpful for you. If you choose to tell the researchers why you are leaving the study, your reasons for leaving may be kept as part of the study record. If you decide to leave the study before it is finished, please tell your study doctor or one of the researchers listed in Section 10 "Contact Information" (below).

7.3 Could the researchers take me out of the study even if I want to continue to participate?
Yes. There are many reasons why the researchers may need to end your participation in the study. Some examples are:

- The researcher believes that it is not in your best interest to stay in the study.
- You become ineligible to participate.
- Your condition changes and you need treatment that is not allowed while you are taking part in the study.
- You do not follow instructions from the researchers.
- The study is suspended or canceled.

8. FINANCIAL INFORMATION

8.1 Who will pay for the costs of the study? Will I or my health plan be billed for any costs of the study?
The study will pay for research-related items or services that are provided only because you are in the study. The investigational study drug, pevonedistat (TAK-924), will be supplied at no cost to you. If you are not sure what these are, see Section 4.1 above or ask the researchers for a list. If you get a bill you think is wrong, call the researchers' number listed in section 10.1.

You or your health plan will pay for all the things you would have paid for even if you were not in the study, like:

- Health care given during the study as part of your regular care
- Items or services needed to give you study drugs or devices
- Monitoring for side effects or other problems
- Deductibles or co-pays for these items or services, and for Docetaxel

If you do not have a health plan, or if you think your health plan may not cover these costs during the study, please talk to the researchers listed in Section 10 below or call your health plan's medical reviewer.

<u>What if I am injured while taking part in this study?</u>
The study team has given you instructions about this research study. It is important that you follow these instructions carefully. If you get sick, have a medical complication, or are injured as a result of your being in the study, call Dr. Gregory Kalemkerian immediately, at 734-647-8902 or 734-936-6267 (24-hour paging). The doctor will either treat you or send you to another doctor for treatment.

You will get free medical care at the UMHS for any hospitalization or ER visits directly caused by the study drug, device, or procedure. The UMHS and the study doctor are responsible for determining whether your condition was the result of your participation in the study.

The UMHS will pay for your treatment only if the need for treatment has been caused by the study drug, device or procedure. This means that you or your health plan must pay for any treatment that is part of your usual medical care or that is related to a medical condition you had before participating in the study.

By signing this form, you do not give up your right to seek payment if you are harmed as a result of being in this study.

8.2 Will I be paid or given anything for taking part in this study?
You will not receive payment or compensation for participating in this study.

8.3 Who could profit or financially benefit from the study results?
Takeda, the company whose product (pevonedistat) is being studied, may benefit in the future.

The University of Michigan and the researchers conducting the study have no financial interest in the outcome of the study. However, the University of Michigan is receiving payment from Takeda to support the activities that are required to conduct the study. No one on the research team will receive a direct payment or increase in salary from Takeda for conducting this study.

Research can lead to new discoveries, such as new tests, drugs, or devices. Researchers, their organizations, and other entities, including companies, may potentially benefit from the use of the data or discoveries. You will not have rights to these discoveries or any proceeds from them.

9. CONFIDENTIALITY OF SUBJECT RECORDS AND AUTHORIZATION TO RELEASE YOUR PROTECTED HEALTH INFORMATION

The information below describes how your privacy and the confidentiality of your research records will be protected in this study.

9.1 How will the researchers protect my privacy?
Your participation will occur at the University of Michigan Cancer Center.

Your data will be kept confidential, to the extent permitted by applicable laws, in the following manner:
•Your name will not be used in any reports about the study
• You will be identified only by a study code: a subject ID number, and initials
• Your identifying information will be kept secure

The sponsor will assign a code number to the study data and may use your initials. Some study data may contain information that could be used (perhaps in combination with other information) to identify you (e.g., initials, date of birth).

The sponsor will use the study data for research purposes to support the scientific objectives of the study. Study data (that does not directly identify you) may be published in medical journals or shared with others as part of scientific discussions.

9.2 What information about me could be seen by the researchers or by other people? Why? Who might see it?
Signing this form gives the researchers your permission to obtain, use, and share information about you for this study, and is required in order for you to take part in the study. Information about you may be obtained from any hospital, doctor, and other health care provider involved in your care, including:

- Hospital/doctor's office records, including test results (X-rays, blood tests, urine tests, etc.)
- Mental health care records (except psychotherapy notes not kept with your medical records)
- Alcohol/substance abuse treatment records
- HIV/AIDS status

- Sexually transmitted disease or other communicable disease status
- All records relating to your condition, the treatment you have received, and your response to the treatment
- Billing information
- Demographic information
- Personal information

There are many reasons why information about you may be used or seen by the researchers or others during or after this study. Examples include:

- The researchers may need the information to make sure you can take part in the study.
- The researchers may need the information to check your test results or look for side effects.
- University, Food and Drug Administration (FDA), and/or other government officials, auditors, and/or the IRB may need the information to make sure that the study is done in a safe and proper manner.
- Study sponsors or funders, or safety monitors or committees, may need the information to:
    - Make sure the study is done safely and properly
    - Learn more about side effects
    - Analyze the results of the study
- Insurance companies or other organizations may need the information in order to pay your medical bills or other costs of your participation in the study.
- The researchers may need to use the information to create a databank of information about your condition or its treatment.
- Information about your study participation may be included in your regular UMHS medical record.
- Federal or State law may require the study team to give information to government agencies. For example, to prevent harm to you or others, or for public health reasons.

The results of this study could be published in an article, but would not include any information that would let others know who you are.

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

9.3 What happens to information about me after the study is over or if I cancel my permission?

As a rule, the researchers will not continue to use or disclose information about you, but will keep it secure until it is destroyed. Sometimes, it may be necessary for information about you to continue to be used or disclosed, even after you have canceled your permission or the study is over.

Examples of reasons for this include:

- To avoid losing study results that have already included your information
- To provide limited information for research, education, or other activities (This information would not include your name, social security number, or anything else that could let others know who you are.)
- To help University and government officials make sure that the study was conducted properly

As long as your information is kept within the University of Michigan Health System, it is protected by the Health System's privacy policies. For more information about these policies, ask for a copy of the University of Michigan "Notice of Privacy Practices". This information is also available on the web at http://www.uofmhealth.org/patient+and+visitor+guide/hipaa. Note that once your information has been shared

with others as described under Question 9.2, it may no longer be protected by the privacy regulations of the federal Health Insurance Portability and Accountability Act of 1996 (HIPAA).

9.4 When does my permission expire?

Your permission expires at the end of the study, unless you cancel it sooner. You may cancel your permission at any time by writing to the researchers listed in Section 10 "Contact Information".

10. CONTACT INFORMATION

10.1 Who can I contact about this study?

Please contact the researchers listed below to:

- Obtain more information about the study
- Ask a question about the study procedures or treatments
- Talk about study-related costs to you or your health plan
- Report an illness, injury, or other problem (you may also need to tell your regular doctors)
- Leave the study before it is finished
- Express a concern about the study

Principal Investigator: [redacted]

You may also express a concern about a study by contacting the Institutional Review Board listed below.

[redacted]

If you are concerned about a possible violation of your privacy or concerned about a study you may contact the University of Michigan Health System Compliance Help Line at 1-866-990-0111.

When you call or write about a concern, please provide as much information as possible, including the name of the researcher, the IRBMED number (at the top of this form), and details about the problem. This will help University officials to look into your concern. When reporting a concern, you do not have to give your name unless you want to.

11. RECORD OF INFORMATION PROVIDED

11.1 What documents will be given to me?

Your signature in the next section means that you have received copies of all of the following documents:

- This "Consent to be Part of a Research Study" document. (*Note: In addition to the copy you receive, copies of this document will be stored in a separate confidential research file and may be entered into your regular University of Michigan medical record.)*
- Other (specify):_____

12. SIGNATURES

Consent/Assent to Participate in the Research Study

I understand the information printed on this form. I have discussed this study, its risks and potential benefits, and my other choices with _____. My questions so far have been answered. I understand that if I have more questions or concerns about the study or my participation as a research subject, I may contact one of the people listed in Section 10 (above). I understand that I will receive a copy of this form at the time I sign it and later upon request. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Consent/Assent for Participating in an Optional Use of Available Tumor Tissue

This project involves optional use of available tumor tissue to look at biomarkers. I understand that it is my choice whether or not to take part in the optional use of my available tumor tissue. I understand that if my ability to consent or assent for myself changes, either I or my legal representative may be asked to re-consent prior to my continued participation in this study.

_____ Yes, I agree to use of my available tumor tissue to look at biomarkers.

_____ No, I do not agree to use of my available tumor tissue to look at biomarkers.

Legal Name: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

Principal Investigator or Designee

I have provided this participant and/or his/her legally authorized representative(s) with information about this study that I believe to be accurate and complete. The participant and/or his/her legally authorized representative(s) indicated that he or she understands the nature of the study, including risks and benefits of participating.

Legal Name: _____

Title: _____

Signature: _____

Date of Signature (mm/dd/yy): _____

PERSONAL CENSUS FORM

UMCC # 2017.063

Name _____ Date _____

The National Cancer Institute requires that The University of Michigan Comprehensive Cancer Center report race and ethnicity information about people who participate in clinical research to ensure that all populations are offered the opportunity to participate.

☐ Check here if you do not wish to provide some or all of the information below.

1. What race do you consider yourself to be? (Please select *one or more*)
   - ☐ American Indian/Alaska Native[a]
   - ☐ Asian[b]
   - ☐ Black or African American[c]
   - ☐ Native Hawaiian or Other Pacific Islander[d]
   - ☐ White[e]
   - ☐ More than one race[f]

2. Do you consider yourself to be Hispanic[g]? ☐ Yes ☐ No

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[a] American Indian or Alaska Native- A person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliation or community attachment.

[b] Asian- A person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent, including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand and Vietnam.

[c] Black or African American- A person having origins in any of the black racial groups of Africa. (Terms such as "Haitian" or "Negro" are sometimes used in addition to "Black" or "African American.")

[d] Native Hawaiian or Other Pacific Islander- A person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

[e] White- A person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

[f] More than one race- (It is preferred that this be selected in addition to the selection of the specific races listed above, but this may also be solely selected.)

[g] Hispanic or Latino- A person of Mexican, Puerto Rican, Cuban, Central or South American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" is sometimes used in addition to "Hispanic" or "Latino."