CLINICAL STUDY PROTOCOL

A Phase I/II Trial of Pevonedistat in Combination with Pembrolizumab in Patients with dMMR/MSI-H Cancers

Indication: PD-1 progressive dMMR/MSI-H cancers
Phase: I/II

Protocol History
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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Common abbreviations used in oncology protocols are provided below. Program-specific or protocol-specific abbreviations must be added to this list, and unnecessary abbreviations removed, as applicable. Abbreviations that are retained should not be changed.

Abbreviation	Term
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
$AUC_{24\ hr}$	area under the plasma concentration versus time curve from zero to 24 hours
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CL	clearance, IV dosing
C_{max}	single-dose maximum (peak) concentration
CNS	central nervous system
CR	complete response
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P_{450}
DLT	dose-limiting toxicity
dMMR	deficient DNA mismatch repair
DNA	deoxyribonucleic acid
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	End of Treatment (visit)
FDA	United States Food and Drug Administration
G-CSF	granulocyte colony stimulating factor
GM-CSF	granulocyte macrophage colony-stimulating factor.
GI	Gastrointestinal
GLP	Good Laboratory Practices

Abbreviation	Term
Hb	Hemoglobin
Hct	Hematocrit
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
IRB	institutional review board
IV	intravenous; intravenously
K_i	inhibition constant
LDH	lactate dehydrogenase
LFT	liver function test(s)
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MRI	magnetic resonance imaging
MSI-H	Microsatellite instability high
MTD	maximum tolerated dose
MUGA	multiple gated acquisition (scan)
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NPO	nothing by mouth
NYHA	New York Heart Association
PCR	polymerase chain reaction
PD	progressive disease (disease progression)
PK	pharmacokinetic(s)
PO	*per os*; by mouth (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
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SC	Subcutaneous
SD	stable disease
$t_{1/2}$	terminal disposition half-life
TGI	tumor growth inhibition

Abbreviation	Term
ULN	upper limit of the normal range
WBC	white blood cell

1. BACKGROUND AND STUDY RATIONALE

1.1 Scientific Background

1.1.1 Disease Under Treatment

Deficient DNA mismatch repair (dMMR) propagates a phenotype of hypermutability known as microsatellite instability (MSI) [1]. This dysfunction is responsible for a number of MSI high (MSI-H) malignancies, among which endometrial, gastric and colorectal cancers are well known [2-4]. Although these are considered ideally suited for immunotherapy due to immunogenic neoantigen production, in reality, only a fraction are responsive. In the case of dMMR/MSI-H colorectal cancer (CRC), among the 15% that responds to immune blockade therapy there is still the risk of developing resistance to this mode of therapy [5].

Several mechanisms exist to enable dMMR/MSI-H tumor survival. One of these is facilitated through the Nedd8-mediated misfolded protein clearance pathway. Neddylation is responsible for the activity of cullin-RING ubiquitin ligases (CRLs), most of which manage crucial cell cycle proteins and may be induced by external stressors including heat shock or proteasome inhibition [6, 7]. Data from MD Anderson Cancer Center[8] supports the notion that the use of Nedd8-activating enzyme inhibitors in combination with immunotherapy would be an effective treatment strategy for dMMR/MSI-H cancers.

To start, analysis of dMMR/MSI-H cell lines with thermal stability profiling demonstrated the presence of more destabilizing mutations compared to microsatellite stable (MSS) cell lines (Fig. 1). Further experimentation performing immunoprecipitation with anti-Nedd8 antibody on transfected FLAG-tagged wild-type or P87S-mutant PTS (a highly destabilizing mutation) support the hypothesis that aggregation of these misfolded proteins can imitate conditions promoting stress-induced neddylation (Fig. 2). Thus dMMR/MSI-H cancers are dependent on the Nedd8-mediated misfolded protein clearance pathway to maintain proteome functionality.

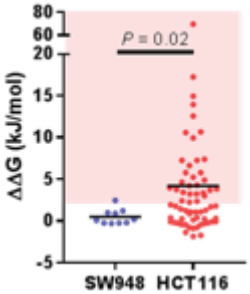


Figure 1. Thermodynamic modeling of mutations in MSI HCT-116 and MSS SW948 cells. A higher ΔΔG represents more destabilization. Shaded region depicts mutations that are significantly destabilizing. Rank-sum test.

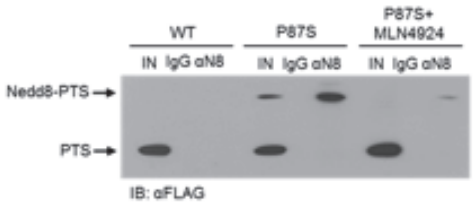


Figure 2. Immunoprecipitation with anti-Nedd8 shows neddylation of mutant, but not WT and P87S-mutant PTS that is blocked by a 24 hour treatment with 1 μM Pevonedistat.

Furthermore, findings from earlier studies inform us that tumors tend to upregulate expression of chaperone proteins to offset the effects of destabilizing mutations [9]. Hsc70 is one such protein folding chaperone, encoded by the *HSPA8* gene that is overexpressed in dMMR/MSI-H tumors (Fig. 3). This chaperone selectively binds destabilizing mutations (Fig. 4). Studies have noted their ability to mitigate toxicity from proteins that tend to cluster [10]. In the event of inadequate functioning chaperone proteins, the cell undergoes the endoplasmic reticulum (ER) stress or an unfolded protein response that culminates in immunogenic cell death (ICD) [11].

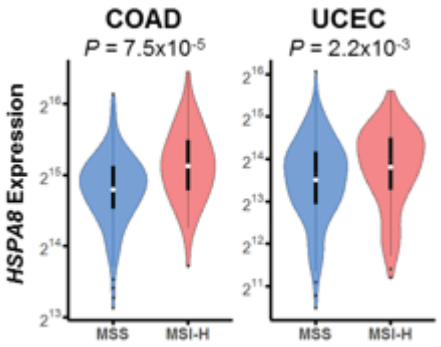


Figure 3. Comparison of HSPA8 gene expression in MSS and MSI colorectal (COAD) and endometrial (UCEC) cancers. White dot indicated median, box indicates interquartile range. Rank-sum test

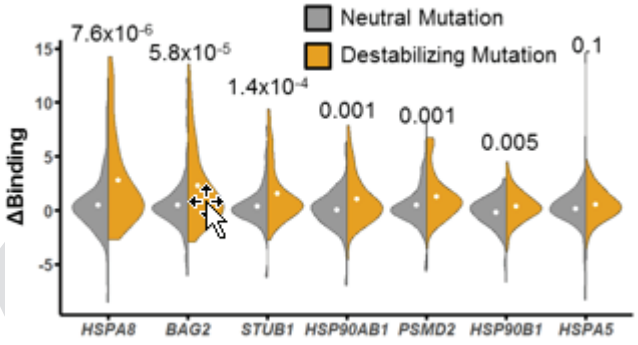
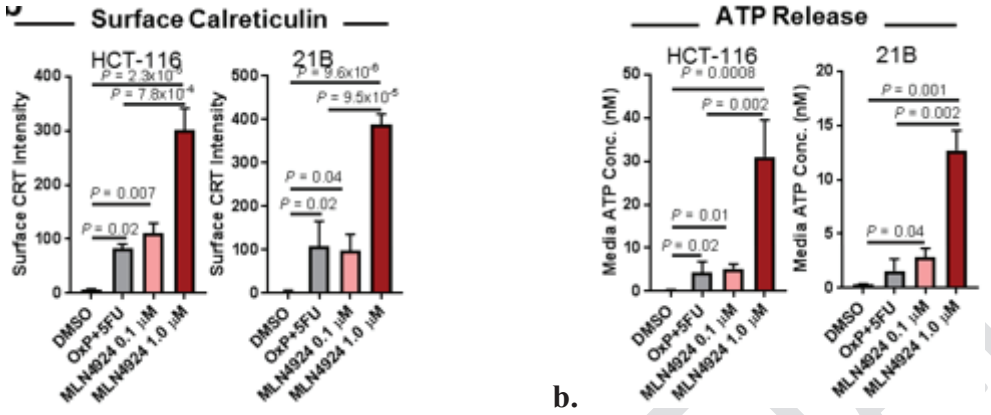


Figure 4. Change in chaperone binding between wild-type and mutant genes based on if a mutation has no effect on stability or is destabilizing. Rank-sum test

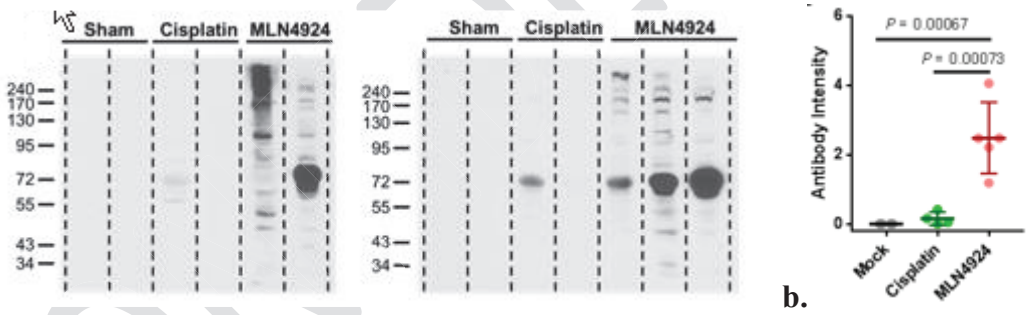
Pevonedistat is a Nedd8-activating enzyme inhibitor that interferes with dMMR/MSI-H cancer cell ability to survive by influencing neddylation and overwhelming the chaperone system ability to clear misfolded proteins. Testing murine endometrial dMMR cancer cell line (designated "21B") and human colon cancer cell line (denoted "HCT-116") after pevonedistat administration revealed the following: markers of ER stress, calreticulin expression and ATP secretion denoting ICD (Fig 5), and rise in cytokines reflecting cytotoxic T-cell recruitment. Likewise, injection of Pevonedistat treated 21B

cells as an anti-tumor vaccine into immunocompetent mice produced more circulating tumor antibodies compared to mice treated with cisplatin or sham PBS (Fig 6*)*.



a. b.

Figure 5. a) Percentage of cells positive for cell surface calreticulin following 24 hours of specified drug treatments. Mean±s.e.m. b) Media ATP concentration following a 24 hour treatment with the specified drugs. Mean±s.e.m. 21b = murine endometrial dMMR cancer cell line, HCT-116 = human colon cancer cell line



a. b.

Figure 6. a) Detection of antibody production against 21B tumor cells (murine endometrial dMMR cancer cell line) in serum from mice (left and right membranes were developed simultaneously for equal exposure). b) Antibody production was quantified from band intensities in 4a

Finally, the ability to enhance immune checkpoint therapy was characterized through treatment of *Msh2*-null 21B tumors treated with monotherapy of anti-PD1 or pevonedistat or a combination of both. While tumor growth was acceptably inhibited by monotherapy, the combination therapy group exhibited markedly decreased tumor growth (Fig 7) and increased CD8 immunostaining compared to pevonedistat monotherapy alone (Fig 8).

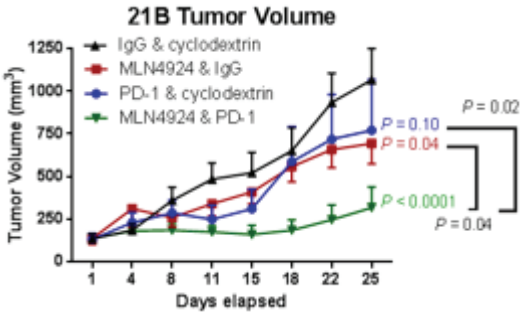


Figure 7. Tumor growth curves for the dMMR 21B mouse cell line treated with PEVONEDISTAT, anti-PD1, or a combination thereof. Mean±s.e.m.; Holm-Sidak correction

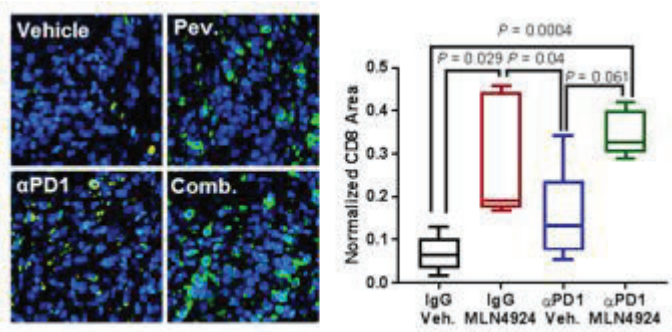


Figure 8. CD8 immunostaining in tumors treated with drug combinations that were quantified as the CD8 staining area normalized to DAPI (nuclei) for total tumor area. Kruskal-Wallis test

In light of all these findings, we propose a clinical trial of Nedd8-activating enzyme inhibitor Pevonedistat in combination with the PD-1 inhibitor, Pembrolizumab, in patients with dMMR/MSI-H cancers.

Combination therapy with pembrolizumab and pevonedistat

The mechanism of action for the two study agents is non-overlaping. However, Pevonedistat is noted to cause AST/ALT elevations or increased bilirubin [12], which is also seen in pembrolizumab. However, it should be noted that the mechanisms of action causing transaminitis or elevation of bilirubin differ between these two agents. However, given this common toxicity this study plans to utilize a 3+3 design to determine RP2D of pevonedistat to use in combination with pembrolizumab.

1.1.2 Study Drug

Pevonedistat (also known as TAK 924 and MLN4924; hereinafter referred to as pevonedistat) is a first-in-class, small molecule inhibitor of neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)-activating enzyme (NAE) under development for the treatment of malignancies. The NEDD8 conjugation (neddylation) pathway is responsible for much of the regulated protein turnover in the cell [13, 14], which is similar to the ubiquitin-proteasome system (UPS). However, UPS is known to regulate a myriad of processes in eukaryotic cells, whereas only a limited number of neddylation substrates have been described to date. VELCADE® (bortezomib) for Injection, a drug that acts by inhibiting the 26S proteasome, has proven utility in the treatment of multiple myeloma and mantle cell lymphoma [15]. Therefore, it is anticipated that other compounds directed against different components of the UPS and/or the NEDD8 conjugation pathway may prove useful in the treatment of malignancies.

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

PD-1 inhibitors, especially pembrolizumab, have been extensively studied in the context of dMMR/MSI-H cancers. At present, pembrolizumab has been approved by the FDA for use in metastatic or unresectable, dMMR/MSI-H CRC with progressive disease following fluoropyrimidine, oxaliplatin and irinotecan treatment as well as for dMMR/MSI-H solid tumors which progressed on prior treatment and do not have satisfactory alternative therapy options.[16] Additional information regarding the agent is available through its current package insert.

1.2 Preclinical Experience with Pevonedistat

Target pharmacology

Pevonedistat is a potent and selective inhibitor of NAE activity (pevonedistat was at least 300- and 1800- fold more selective for NAE than for the closely related ubiquitin activating enzyme and sumo activating enzyme, respectively). Pevonedistat treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines derived from acute leukemias, lymphomas, multiple myeloma, and a range of solid tumor types. Changes in protein levels observed in cultured cells treated with pevonedistat were consistent with the inhibition of NAE, in particular a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CDL substrates, including NFE2-related factor 2 (Nrf2) and chromatin-licensing and DNA-replication factor-1 (Cdt-1). In most cell lines evaluated, NAE inhibition by pevonedistat led to DNA re-replication and accumulation of cells in the S phase of the cell cycle; this resulted in DNA damage and subsequent cell death through apoptosis [17-19]. When administered in combination with hypomethylating agents azacitidine and decitabine demonstrated synergistic activity in AML cell lines.

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

Safety pharmacology

In vitro assay results indicated a low risk for human ether-à-go-go related gene (hERG) channel inhibition by pevonedistat (K_i=17.3 μM) or its 3 major circulating metabolites.

A non-GLP-compliant PO toxicity study was performed in Sprague Dawley rats dosed with 150 mg/kg pevonedistat on Days 1, 3, and 5. Minimal to mild pulmonary artery adventitial

hyperplasia and correlative increases in pulmonary artery pressure were observed at 24 hours postdose. However, there was no correlation observed between severity of the microscopic lesions and increases in pulmonary artery pressure. This finding was not observed in rats dosed IV or SC in studies up to 3 months in duration, so the relevance of this finding to clinical safety is not known.

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

Toxicology

The systemic toxicity of pevonedistat was assessed in GLP-compliant repeat-dose studies in rats and dogs. Pevonedistat was administered via a 30-minute IV infusion or by SC injection for 2 cycles (5 days of dosing followed by a 14-day nondosing period) or for 5 cycles (4 doses administered every other day followed by a 14-day nondosing period). The DLTs in the 2-cycle studies for both species were GI toxicity and bone marrow and lymphoid tissue depletion. In tolerated doses in both species, adverse effects included GI tract injury with emesis (dogs only) and abnormal excreta, hematologic alterations, and an acute phase response (increased fibrinogen and decreased albumin). Increased new trabecular bone formation was observed in the 2 cycle study, while decreased trabecular bone formation was observed in the 5-cycle study and was considered an adverse finding. Microscopic observations in both species included karyomegaly, apoptosis, and increased mitotic figures occurring in rapidly dividing tissues, including the intestinal tract and bone marrow. Most adverse effects were resolving or had resolved after a 2 week recovery period.

Pevonedistat did not result in lethality in either of the 5-cycle studies. The primary adverse test article related effects in IV dosed dogs included an acute phase response (increased body temperature, decreased albumin, increased globulin, increased monocytes and neutrophils, and increased fibrinogen levels); neutrophilic infiltrates in multiple tissues (liver, intestines, spleen, trachea, Peyer patches, and gallbladder); 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 in both rats and dogs.

Pevonedistat did not induce any local tissue response when administered by IV infusion to rats or dogs.

Pevonedistat was not mutagenic in the bacterial reverse mutation assay (Ames assay).

Microscopic changes were observed in male and female reproductive organs in the GLP compliant repeat-dose toxicology studies in both dogs and rats, therefore pevonedistat likely represents a substantial reproductive and developmental hazard.

Non clinical pharmacokinetics

Pevonedistat was extensively partitioned into RBCs in mice, rats, dogs, monkeys, and humans, most likely as a result of the binding to carbonic anhydrase (CA) in the RBCs. The partitioning was species dependent and concentration dependent and was saturable. Pevonedistat was highly bound in whole blood and plasma of mice, rats, dogs, monkeys and humans. No metabolite unique to humans was observed in vitro. In vitro, pevonedistat is predominantly metabolized by the cytochrome P450 (CYP) isozyme 3A4. There is potential for drug drug interactions (DDIs) if pevonedistat is coadministered with drugs that are CYP3A inhibitors or inducers. Pevonedistat is neither an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC_{50} > 100 μM and Ki > 50 μM) nor an inducer of CYP1A2, 2B6, or 3A4/5 (at concentrations up to 30 μM), but is a weak inhibitor of CYP2B6 and 2C8 (IC_{50} = 97.6 and 23.1 μM, respectively). The major elimination pathway of pevonedistat in animals is through the hepatic route. Pevonedistat is a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2) in Caco 2 cells. Pevonedistat is also a weak inhibitor of P-gp (IC_{50} = 41.2 to 56.0 μM) and BCRP (IC_{50} = 6.3 μM), but not of MRP2 (IC_{50} > 200 μM). Additionally, pevonedistat is not a substrate for organic anion-transporting proteins (OATPs).

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

1.3 Clinical Experience with Pevonedistat

To date, the pevonedistat clinical development program consists of 14 clinical studies in patients with advanced malignancies.

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 [6].
- Study C15002 in patients with lymphoma or multiple myeloma [20].
- Study C15003 in patients with AML, high-grade myelodysplastic syndrome (MDS), or acute lymphoblastic leukemia (ALL) [21].
- Study C15005 in patients with melanoma [22].

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

The schedule for pevonedistat infusion of Days 1, 3, and 5 was chosen for further studies. The maximum tolerated dose (MTD) for that schedule for patients with AML in Study C15003 was determined to be 59 mg/m2, and the MTD for patients with solid tumors in Study C15001 was determined to be 67 mg/m^2.

Current development is focused on pevonedistat in combination with standard clinically available therapies in hematologic malignancies and solid tumors.

- Study C15009 (phase 1b) evaluated the maximum tolerated dose (MTD) of pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine

(administered on a 5-on/2-off [weekend]/2-on schedule) in a 28 day treatment cycle in elderly patients with treatment-naïve AML and is completed [23].

- Study C15010 (phase 1b) is complete; combination therapy also included pevonedistat + gemcitabine [24, 25].

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

- Pevonedistat-2001 (phase 2) evaluated the efficacy and safety of pevonedistat 20 mg/m^2 on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitadine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28 day versus single-agent azacitidine in patients with higher-risk MDS (HR MDS), higher-risk chronic myelomonocytic leukemia (CMML), and low-blast AML. The study is completed, and the final results have been reported. The combination of pevonedistat and azacitidine had a comparable safety profile to azacitidine alone [26].

– Pevonedistat-3001 (phase 3) is evaluating the efficacy and safety of Pevonedistat 20 mg/m^2 on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28 day versus single-agent azacitidine in patients with higher-risk MDS (HR MDS), higher-risk chronic myelomonocytic leukemia (CMML), and low-blast AML. The study is currently is fully enrolled.

- Pevonedistat-1012 (phase 1) is investigating pevonedistat as a single agent and in combination with azacitidine in adult East Asian patients with AML or MDS is complete and ongoing.

- Study Pevonedistat 1013 (phase 1) (Part A: Absorption, distribution, metabolism, and excretion [ADME] is complete). Part B, combination therapy, completed enrollment and is ongoing.

- Study Pevonedistat-1014 (phase 1) Part A, QTc, and Part B, combination therapy, completed enrollment and is ongoing

- Study Pevonedistat-1015 (phase 1) Part A, DDI, and Part B, combination therapy, completed enrollment and is ongoing

- Study Pevonedistat-1016 (phase 1) in patients with higher risk (HR) MDS, chronic myelomonocytic leukemia (CMML), and AML who have renal or hepatic impairment is ongoing.

In addition, supportive studies investigating pevonedistat in patients with organ impairement, Drug-drug interaction effect, QTc interval effect and Mass Balance, Pharmacokinatics and metabolism of pevonedistat have been completed and reported.

As of 22 January 2019, an estimated 647 patients received active treatment with pevonedistat based upon exposure data from completed and ongoing studies, including 99 patients from Study P3001. Notably, Study P3001 is an open-label study; however, Takeda staff or its designee that are directly involved in the study are blinded to the treatment assignments. As such, the current number of patients randomized to pevonedistat plus azacitidine versus azacitidine alone is unknown; however, it is estimated that 99 of the total 198 patients currently enrolled received pevonedistat based on the randomization scheme (1:1) described in the protocol. An estimated 372 patients with hematologic indications and 275 patients with solid tumor indications have received pevonedistat.

1.3.1 Clinical Pharmacokinetics

Plasma concentrations of pevonedistat declined in a bi-exponential manner at the end of IV infusion, with little or no drug accumulation following intermittent dosing or once-daily dosing for 5 consecutive days of a 21 day cycle. Mean terminal disposition t1/2z was estimated to be approximately 10 hours (range 7.7-15.2) across doses and schedules. Consistent with in vitro data, pevonedistat is extensively partitioned in human blood (mean blood-to-plasma concentration ratio of approximately 65) with whole blood and plasma kinetics declining in parallel over time. Pevonedistat generally exhibited linear PK over the dose range studied. Observed interindividual variability (IIV) was generally moderate with 18% to 41% coefficient of variation (CV) for maximum concentration (Cmax), 12% to 56% CV for area under the plasma concentration-time curve from time zero to 24 hours postdose (AUC_{24}), and 15% to 33% CV for the area under the plasma concentration-time curve from time zero to the end of the dosing interval when pevonedistat was administered on Days 1, 3, and 5. Body size influences pevonedistat systemic clearance 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.

Population pharmacokinetic (PK) analysis was conducted using data from pevonedistat single-agent studies (C15001, C15002, C15003, and C15005) and pevonedistat in combination with SOC chemotherapy (C15009 and C15010) in patients with solid tumor or hematologic malignancies. The database contained 335 subjects contributing 3768 PK observations over the pevonedistat dose range of 15 - 278 mg/m^2. Pevonedistat plasma concentration-time profiles were well described by a 2-compartment model with linear elimination. Coadministration with azacitidine did not appear to affect the CL of pevonedistat. Race, sex, age, tumor type (hematologic vs solid), mild or moderate renal impairment (creatinine clearance [CrCL] ≥30 mL/minutes), and mildly impaired liver function, to the extent represented in this dataset, had no impact on pevonedistat PK. An open-label drug-drug interaction (DDI) Study C15011 evaluated the CYP3A-mediated inhibitory effects of fluconazole and itraconazole on pevonedistat PK in patients with advanced solid tumors. The results indicated that itraconazole, a strong CYP3A/P-gp inhibitor, and fluconazole, a moderate CYP3A inhibitor, had no clinically meaningful effects on pevonedistat PK. On the basis of these findings, use of CYP3A/P-gp inhibitors in patients receiving pevonedistat is permitted.Study Pevonedistat-1012 is a phase 1/1b, open-label study of pevonedistat as single agent and in combination with azacitidine in adult East Asian patients with AML or MDS enrolled in Japan, South Korea, and Taiwan. Pevonedistat 20 mg/m^2 in combination with 75 mg/m^2 azacitidine was determined to be the MTD/recommended phase 2 dose in Asian patients. The preliminary analysis indicated that the systemic exposure of pevonedistat was similar among major East Asian races, ie, Japanese, Korean, Chinese. Furthermore, the systemic exposures of pevonedistat was comparable between East Asian and Western patients. These results support the same RP2/3D of pevonedistat in combination with azacitidine in global patient population.

Additional data from 11 patients who completed protocol-specified dosing and PK evaluations indicated that pevonedistat systemic exposures following IV administration at 20 mg/m^2 in the presence of itraconazole were similar to those in the absence of itraconazole. On the basis of these results, moderate and strong CYP3A inhibitors and P-gp inhibitors can be used in patients receiving pevonedistat. For individual studies in the

pevonedistat clinical program, reference should be made to the respective protocols for specific information relating to excluded and permitted medications.

For detailed information please consult the current 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 15 to 261 mg/m^2 across various studies (single-agent, phase 1 pevonedistat trials and DDI Study C15011).

For detailed information please consult the current IB.

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

For detailed information please consult the current IB.

1.3.3.1 Phase 1 Monotherapy Studies

Overall, 99 patients with advanced solid tumors or melanoma in Study C15001 and Study C15005 were treated with single-agent pevonedistat at doses ranging from 25 to 278 mg/m^2. Common AEs (reported by ≥ 25% of patients) were fatigue, nausea, anemia, decreased appetite, vomiting, diarrhea, myalgia, constipation, arthralgia, dizziness, and peripheral neuropathy. DLTs included increased LFTs, increased creatinine, acute renal failure and 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 reported 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 renal failure acute (at 209 mg/m^2 in Study C15005).

A total of 128 patients with hematologic malignancies (lymphoma, multiple myeloma, AML, MDS, or ALL) in Study C15002 and Study C15003 were treated with single-agent pevonedistat at doses ranging from 25 to 261 mg/m^2. Common AEs (reported by ≥ 25% of patients in either study) were ALT increased, anemia, AST increased, chills, constipation, decreased appetite, diarrhea, dizziness, dyspnea, fatigue, febrile neutropenia, headache,

muscle spasms, myalgia, nausea, peripheral edema, pyrexia, and vomiting. DLTs included increased LFTs, febrile neutropenia, muscle spasms, thrombocytopenia, acute renal failure, orthostatic hypotension, cardiac failure, rash morbilliform, GI necrosis, hypotension, lactic acidosis, and myocardial ischemia. Deaths on study that were considered related to study treatment (all in Study C15003) included 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).

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

In Study C15003, responses (CRs and PRs) were observed in a variety of patient settings, including postallogeneic transplant, therapy-related AML, and primary refractory AML [27]. Although some of the responses were of relatively short duration, 1 patient each in the 44 mg/m^2 cohort of Schedule A, the 83 mg/m^2 MTD cohort of Schedule B, and the 25 mg/m^2 cohort of Schedule A achieved a remission for 12.3, 10.1, and 5.1 months, respectively. Another patient had stable disease (SD) for 8 cycles, then a PR, followed by a CR for a total of 2.7 months. All 13 patients who received treatment for 5 or more cycles achieved SD or better, ranging from 2.56 to 13.44 months. The duration of SD or better was considered clinically meaningful if the patient had SD or better at Cycle 4 Day 21 and proceeded to Cycle 5.

1.3.3.2 Phase 1 Combination Studies

1.3.3.2.1 C15009

Study C15009 was a phase 1b study evaluating the MTD of pevonedistat on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28-day treatment cycle in patients 60 years of age or older with treatment naïve AML who are unlikely to benefit from standard induction therapy. As of 22 January 2017, enrollment had completed and as of January 2019 no patients remain on study. Data are available in CSR addendum 1 for 64 patients enrolled in the study who received at least 1 dose of pevonedistat in combination with azacitidine; the median number of treatment cycles overall for the MTD pevonedistat dose cohort (20 mg/m^2) was 4.0 (range 1-33 cycles). The most common events (reported by ≥ 25% of patients) were constipation (48%), nausea (42%), fatigue (42%), anemia (41%), febrile neutropenia and thrombocytopenia

(both 31%), decreased appetite (30%)and pyrexia (27%). A total of 46 (72%) patients experienced at least 1 SAE including: febrile neutropenia (27%); pneumonia (14%); AML (11%). A total of 22 patients (34%) overall experienced at least 1 TEAE resulting in discontinuation. Eleven patients died during treatment or within 30 days of the last dose of study drug); none assessed as related to study treatment. Five of the deaths were due to PD, 2 were due to multiple organ dysfunction syndrome (multi-organ failure), and 1 was due to sepsis. Six patients were assessed as having died from PD or AML.PEVO PK was not altered by the addition of AZA.

Overall, responses of CR, CRi, and PR were observed in 31 out of 61 (51%) of patients treated at the MTD of the safety population and 31 out of 52 patients (60%) of patients in the MTD response-evaluable population. These responses were seen regardless of low or high myeloblast count at baseline or disease characteristics, de novo or secondary AML, and cytogenetic risk category.

1.3.3.2.2 C15010

Study C15010 was a phase 1b study evaluating the MTD of pevonedistat plus standard chemotherapy, in patients with solid tumors. As of 22 January 2016, enrollment was completed; 2 patients remain on study as of January 2018. The treatment arms are:

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

Patients received pevonedistat with docetaxel (22 in arm 1), carboplatin+paclitaxel (26 in arm 2), or gemcitabine (10 in arm 3), in 21-day (arms 1 and 2) or 28-day (arm 3) cycles. A lead-in cohort (arm 2a, n = 6) determined the arm 2 carboplatin dose. Dose escalation

proceeded via continual modified reassessment. The MTD for pevonedistat was 25 mg/m^2 (arm 1) or 20 mg/m^2 (arm 2); arm 3 was discontinued due to poor tolerability. Fifteen (23%) patients experienced dose limiting toxicities during cycle 1 (grade ≥3 liver enzyme elevations, febrile neutropenia, and thrombocytopenia), managed with dose holds or reductions. Drug related adverse events (AEs) occurred in 95% of patients. Most common AEs included fatigue (58%), followed by nausea (50%), anemia (41%), constipation and diarrhoea (each 34%), aspartate aminotransferase increased (31%), vomiting (30%), alanine aminotransferase increased (28%), alopecia (27%).. One drug-related death occurred in arm 3 (febrile neutropenia). Pevonedistat exposure increased when co-administered with carboplatin+paclitaxel; no obvious changes were observed when co-administered with docetaxel or gemcitabine. Among 54 response-evaluable patients, two had complete responses (arm 2) and 10 had partial responses (three in arm 1, one in arm 2a, six in arm 2); overall response rates were 16% (arm 1) and 35% (arm 2). High ERCC1 expression correlated with clinical benefit of pevonedista-t+carboplatin+paclitaxel. [28]

1.3.3.2.3 C15011

In Part A of Study C15011, patients receive a single dose of pevonedistat given as an IV infusion on Day 1 and Day 8, and either concomitant oral fluconazole or itraconazole on Day 4 through Day 10. After completion of the drug-drug interactions (DDI) assessments (including a washout period of at least 2 weeks from the last dose of fluconazole or itraconazole), patients could continue treatment with pevonedistat in combination with standard-of-care agents (either docetaxel or the combination of carboplatin and paclitaxel; Part B). As of 22 January 2017 enrollement was completed, 36 of the 51 patients enrolled in Study C15011 continued into Part B of the study In Part B, the most common TEAE overall in the pevonedistat + docetaxel arm was dehydration (48%), followed by fatigue and decreased appetite (43% each); stomatitis, neutropenia, and oedema peripheral (35% each); nausea, diarrhoea, and hypotension (30% each). The most common TEAEs in the pevonedistat + carboplatin/paclitaxel arm were nausea and vomiting (54% each), followed by fatigue, diarrhoea, and constipation (38% each); anaemia and neuropathy peripheral (31% each).

None of the SAEs reported during Part A was assessed as related to treatment. In Part B, the only SAEs reported in more than 1 patient were nausea and vomiting (2 patients each) in the pevonedistat+ carboplatin/paclitaxel arm and pneumonia and hypotension (2 patients each) in the pevonedistat + docetaxel arm. A total of 7 patients (14%) overall experienced at least 1 TEAE resulting in study drug discontinuation during Part A and 8 (22%) patients in Part

B. In Part B, 1fatal AE was considered to be treatment-related (respiratory failure); 15 patients were assessed as having died from causes related to the disease under study or associated complications.

The ORR in Response evaluable patients was 10.5% for pevonedistat+docetaxel and 22.2% for pevonedistat + carboplatin/paclitaxel (2 patients in each treatment arm). The overall median duration of response was 6.26 months, with a longer duration in the pevonedistat + carboplatin/paclitaxel arm (8.46 months) compared with the pevonedistat+docetaxel arm (4.07 months). Clinical benefit (defined as PR/SD ≥5 cycles) was observed in 10 patients. A broad variety of tumor types were represented, and clinical benefit was observed despite prior exposure to a platin or a taxane.

Pevonedistat-1012

In the phase 1 Study Pevonedistat-1012, patients are enrolled in 1 of 4 treatment arms:

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

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

Twenty three patients received therapy (mean, 15.2 doses; median, 8.0 doses) for a total of 118treatment cycles (mean, 5.1 cycles; median, 3.0 cycles).

Overall, the most common AEs (occurring in at least 30% of patients [7 patients overall]) were constipation (57%), nausea and vomiting and pneumonia (each 39%), febrile neutropenia and stomatitis (each 35%), and diarrhea (30%). Fifteen (65%) patients reported an SAE during the study. Except for febrile neutropenia (single-agent pevonedist, 3 patients) and pneumonia (single agent pevonedistat, 6 patients; combination treatment, 1 patient), no other SAE was reported by more than 1 patient. Three deaths occurred during treatment of within 30 days of receiving last dose of study drug and were assessed as not related to the study treatment. Final efficacy data are not available at this time.

1.3.3.2.4 Pevonedistat-2001

This ongoing, phase 2 study is evaluating the efficacy and safety of pevonedistat+azacitidine versus single-agent azacitidine in patients (aged 18 years and older) with HR MDS, CMML, and low blast AML. With a 28-day treatment cycle, pevonedistat is administered on Days 1, 3, and 5 at a starting dose of 20 mg/m^2, with azacitidine at a starting dose of 75 mg/m^2 administered on Days 1 through 5, 8, and 9. As of January 2019, 58 patients were treated with the combination of pevonedistat+azacitidine, and 62 patients received azacitidine alone.

As of 22 January 2019, a total of 58 patients were ongoing in the study in the combination arm [26]. The most common AEs ≥ grade 3 reported in the combination group were neutropenia (33%), febrile neutropenia (26%), anemia (19%), and thrombocytopenia (19%).. On-study deaths occurred in 9% of patients in the combination arm, compared to 16% of patients receiving only azacitidine (n=53). Among the 39 evaluable patients receiving both pevonedistat and azacitidine, ORR was 71% with CR or 45%.

1.3.3.2.5 Pevonedistat-3001

As of 22 January 2020, 443 patients were enrolled and 433 (98%) patients reported at least 1 TEAE. The most common AEs reported were constipation (159 patients [36%]), anemia (135 patients [30%]), neutropenia (132 patients [30%]), nausea (125 patients [28%]), and thrombocytopenia (120 patients [27%]). The most frequently reported SAEs were febrile neutropenia (64 patients [14%]), pneumonia (46 patients [10%]), pyrexia (19 patients [4%]), and anemia (18 patients [4%]). The most frequently reported TEAEs leading to study drug discontinuation were pneumonia (10 patients [2%]), septic shock (9 patients [2%]), febrile neutropenia and thrombocytopenia (each, 6 patients [1%]). Five on-study deaths occurred that were considered related to treatment, 2 patients with septic shock, 1 patient each for the following: bronchopulmonary aspergillosis, abdominal sepsis, and soft tissue necrosis.

Efficacy data are not available at this time.

1.4 Additional Safety Considerations

1.4.1 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, Millennium Pharmaceuticals, Inc. 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.

Nonclinical investigative activities were undertaken to better understand the potential physiology behind the C1D1 events observed with pevonedistat dosing. As summarized in the latest IB, a model in which a minimally toxic, single dose of pevonedistat was administered with TNFα had several hallmarks associated with septic and/or cytokine-induced shock. The overall time course and target organs affected in this nonclinical model also appeared to closely mimic those observed in clinical C1D1 events at single agent doses ranging from 110 to 278 mg/m^2.

In October 2012, a revised risk mitigation strategy limiting the dose to no higher than 50 mg/m^2 for dosing on Days 1, 3, and 5 and no higher than 100 mg/m^2 for dosing on Days 1, 4, 8, and 11 or 1, 8, and 15 for all studies for single agent administration was implemented across the pevonedistat program. As of January 2019, approximately 436 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 to 20 mg/m^2 in combination with a CYP3A inhibitor.

The Days 1, 3, and 5 schedule for pevonedistat infusion was chosen for further studies. The MTD for that schedule for patients with AML in Study C15003 was determined to be 59 mg/m^2, and the MTD for patients with solid tumors in Study C15001 was determined to be 67 mg/m^2.

1.4.2 Guidance for Clinical Assessment and Management of Hemodynamic Compromise

Because of 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. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. For those patients for whom there is a

concern of dehydration, the following guidance for rehydration before pevonedistat dosing may be considered: 500 mL/hour of 0.5 N saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate. 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 based on the patient's risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines. Patients who experience signs and symptoms of hemodynamic compromise after pevonedistat dosing (eg, tachycardia, hypotension, orthostasis, and changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care, including hospitalization as clinically indicated.

1.4.3 Increases in Serum Creatinine

At current doses equal to or below 100 mg/m^2 on a Day 1, 3, and 5 or a Day 1, 4, 8, and 11 schedules, there have been reports of changes in serum creatinine from baseline levels of Grade 0 to Grade 1, and from baseline levels of Grade 1 to Grade 2.

1.4.4 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 following administration of pevonedistat in patients with advanced malignancies receiving pevonedistat as a single agent and in combination with standard of care cytotoxic therapies. Among the single-agent studies, one patient in Study C15001 with metastatic colon cancer experienced a Grade 4 adverse event related to liver function analyses (alanine aminotransferase increased). In Study C15009, in patients with AML treated with pevonedistat in combination with azacitidine, Grade 4 increases for adverse events related to liver function analyses occurred in 2 patients as DLTs (alanine aminotransferase increased, aspartate aminotransferase increased). A third patient in Study C15009 experienced a Grade 4 adverse event (aspartate aminotransferase increased) that was not assessed as a DLT. In Study C15010 in patients with solid tumors treated with pevonedistat in combination with docetaxel, gemcitabine, or carboplatin plus paclitaxel, and also in Study C15011, a drug-drug interaction study, adverse events related to liver function analyses up to Grade 3 were observed.

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. One patient was discontinued from study C15010 because of LFT elevations.

1.4.5 Drug Drug Interactions (DDIs)

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 completed DDI studies, administration of pevonedistat with CYP3A inhibitors and P-gp and BCRP inhibitors is permitted.

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.

For detailed information please consult the current IB.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- For Phase I: determine safety and phase II dose of pevonedistat in combination with pembrolizumab
- To assess the efficacy of Pevonedistat in combination with Pembrolizumab in patients with dMMR/MSI-H cancers.

2.2 Secondary Objectives:

- To assess additional efficacy endpoints of the combination of Pevonedistat and pembrolizumab in dMMR/MSI-H cancers
- To assess the safety of Pevonedistat and pembrolizumab in the dMMR/MSI-H patient cohort.
- To assess the pharmacodynamics impact of Pevonedistat and pembrolizumab on

tumor and immune-related components.

2.3 Exploratory Objectives:

- Immune context evaluation of tumor microenvironment
- Determine clinical benefit
- Evaluate pevonedistat pharmacokinetics and resistance mechanisms in combination therapy

3. STUDY ENDPOINTS

3.1 Primary Endpoints

- Phase I: To identify the RP2D of pevonedistat when combined with pembrolizumab
- Phase II: Objective response (PR or CR) as measured with iRECIST v1.1

3.2 Secondary Endpoints

a. To analyze the pharmacodynamics impact of pevonedistat by evaluating changes in protein misfolding between pre-treatment and on-treatment tumor biopsies
b. PFS (by iRECIST v1.1)
c. Duration of response
d. OS
e. Safety

3.3 Exploratory Endpoints

a. To evaluate immune context of the tumor microenvironment at various time points in treatment course
b. clinical benefit rate (CR+PR+SD by iRECIST v1.1)
c. To evaluate pharmacokintetics of pevonedistat in combination with pembrolizumab
d. To analyze potential mechanisms of anti-PD1/pevonedistat combination therapy resistance/sensitivity by evaluating such markers as neoantigen burden, destabilizing mutation burden, and immune microenvironment characteristics

from pre-treatment tumor biopsies and changes from pre-treatment and on-treamtent tumor biopsies.

e. To analyze potential mechanisms of anti-PD1/pevonedistat combination therapy resistance/sensitivity by evaluating immunological changes in peripheral blood and microbiome diversity and immune-conducive signatures.

f. To evaluate RNA signatures of gene expression and correlate them with patient response on study

4. STUDY DESIGN

4.1 Overview of Study Design

This clinical trial will be a single-arm, non-randomized, open-label two stage phase I/II study of pembrolizumab and pevonedistat in dMMR/MSI-H cancers. All patients are required to have prior progressive disease on prior anti-PD1 therapy.

This study will follow a 3+3 dose escalation design for the phase I portion of the study (fig 9) to determine RP2D. Therefore, a minimum of 3 subjects will be enrolled in each dose cohort:

• If 0 out of the 3 subjects in a dose cohort experience a DLT during the DLT evaluation period, dose escalation may proceed to the next planned level.
• If 1 of the 3 subjects in any dose cohort experiences a DLT during the DLT evaluation period, that dose cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose cohort experiences a DLT, dose escalation may proceed to the next planned dose level.
• If 2 or more subjects in a dose cohort experience a DLT during the DLT evaluation period, the MTD will have been exceeded and no further subjects will be enrolled into that dose cohort. A previous lower dose cohort or an intermediate dose cohort may be explored.
- If 0/3 patients experience DLTs at the highest dose level, this will be declared RP2D

No intra-patient dose escalation will occur. Dose levels for pevonedistat are described in the Table 1. General schema for the study is outlined in figure 10. Determination of MTD and R2PD is outlined in figure 9. The MTD is defined as the highest dose with the DLT rate ≤ 1/6. The RP2D will represent the highest dose level at which the MTD is not exceeded. Once R2PD is determined, phase 2 portion of the study may proceed according to the study schema. Patients included at the R2PD in the phase I portion of the study will be included as part of the planned enrollment in the phase II portion of the study for enrollment purposes.

Table 1. Pevonedistat Dose Levels

Level -2	10 mg/m^2
Level -1	15 mg/m^2
Level 1 (starting dose level)	20 mg/m^2
Level 2	25 mg/m^2

Study agents will be dosed as follows:

- Pevonedistat starting at 20 mg/m^2 IV on days 1, 3, and 5 of a 21 day cycle. Dose escalation will proceed based on criteria described above to determine RP2D.
- Pembrolizumab 200 mg flat dose IV every 3 weeks

Figure 9. Phase 1b 3+3 Design

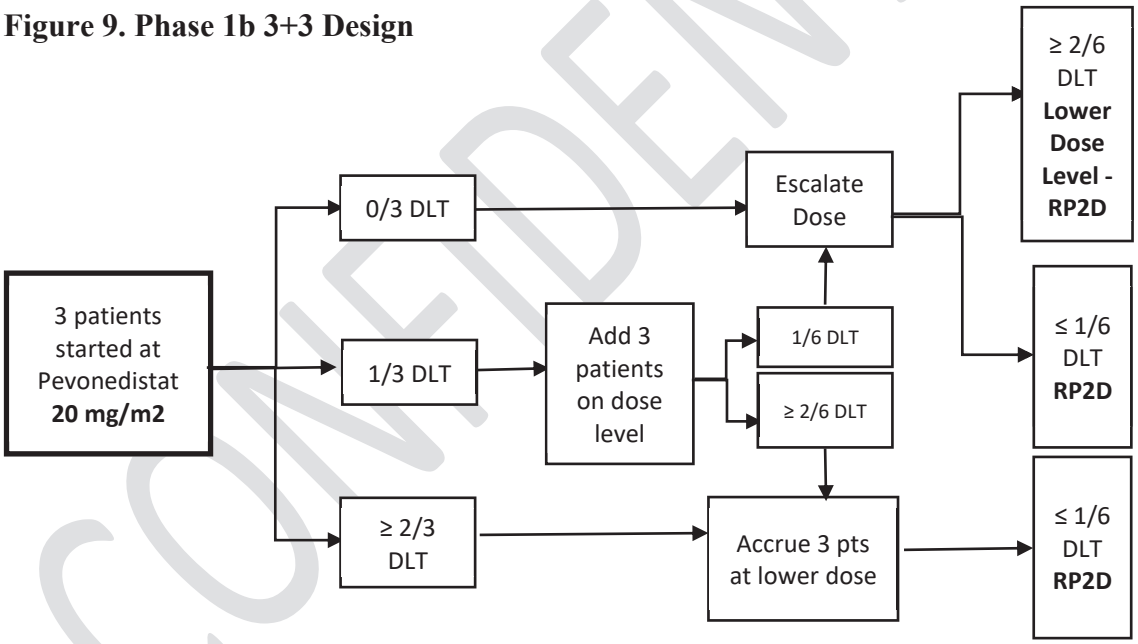
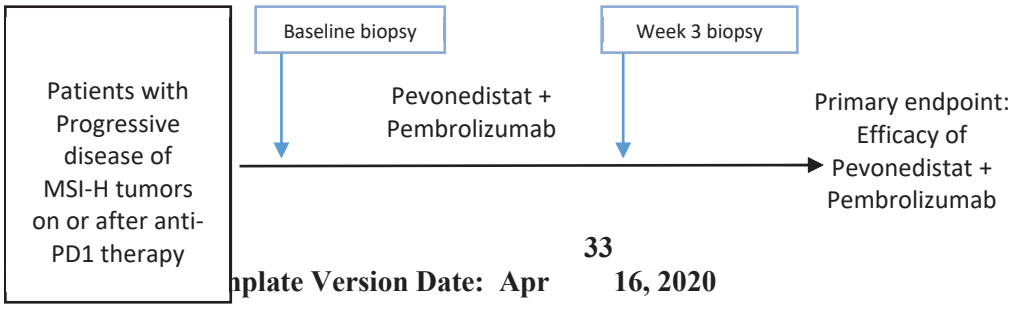


Figure 10. Study Schema



Study specific procedures for each visit are outline in the Schedule of Events (Appendix 6).

4.2 Number of Patients

In order to provide RP2D, we plan to enroll on a 3+3 design with approximately 3-6 patients per cohort followed by a phase II two stage design in which 11 to 21 patients will be enrolled. Approximately 14-39 patients will be enrolled overall in the study to evaluate initial efficacy estimate of the proposed drug combination

4.3 Duration of Study

Anticipated enrollment will be 1 to 1.5 patients per month and thus full enrollment will take 22 months with an additional 6 months for further followup following the last enrolled patient.

5. STUDY POPULATION

5.1 Inclusion Criteria

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

1. Male or female patients 18 years or older.

2. Patients must have metastatic or locally advanced unresectable solid tumor

3. Tumor that is deficient in mismatch repair (dMMR) or microsatellite instability high (MSI-H) as determined by one of three methods:
    - Immunohistochemistry determined dMMR by complete loss of MLH1, PMS2, MSH2 or MSH6
    - PCR determined microsatellite instability at >30% of tested microsatellites
    - Next-generation determined MSI-H based upon instability at multiple microsatellites as determined by the specific next generation sequencing panel
4. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1.
5. Clinical laboratory values within the following parameters:

    a. Hemoglobin ≥8 g/dL (may transfuse to achieve this threshold)

    b. ANC ≥ 1,500/mm^3

c. Platelet count ≥ 100,000/mm^3

d. Albumin > 2.7 g/dL

e. Total bilirubin ≤ 1.5 x upper limit of normal (ULN) except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤ 3 x ULN of the direct bilirubin.

f. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3.0 × ULN

g. Creatinine clearance ≥ 30 mL/min according to MD Anderson standard, automated laboratory calculation.

6. HIV patients may be considered as long as they meet the following criteria:
   - CD4 count > 350 cells/mm3
   - Undetectable viral load
   - No history of AIDS-defining opportunistic infections
7. Female patients who:
   - Are postmenopausal (see Appendix 4 for definition) for at least 1 year before the screening visit, OR
   - Are surgically sterile, OR

   If they are of childbearing potential:

   - Agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception (see Appendix 5), at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug (female and male condoms should not be used together), or
   - Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

   Male patients, even if surgically sterilized (ie, status postvasectomy), who:

- Agree to practice effective barrier contraception during the entire study treatment period and through 4 months after the last dose of study drug (female and male condoms should not be used together), or

- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [eg, calendar, ovulation, symptothermal, postovulation methods for the female partner] withdrawal, spermicides only, and lactational amenorrhea are not acceptable methods of contraception.)

8. Voluntary written consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

9. Demonstrated prior progression on or after anti-PD1/L1 based therapy by radiographic progression. The potential for psuedoprogression should be excluded by concurrent tumor marker (for example carcinoembryonic antigen) or ctDNA elevation, or clinical symptom progression, or short interval repeat imaging confirming progression. (if uncertain if patient meets eligibility please discuss with study PI)
    - Must have received at least 2 doses of a PD1/PD-L1 inhibitor
    - Progressive disease either during therapy or within 2 months of last dose of therapy.
10. Measureable disease by iRECIST v1.1 by treating investigator or study PI.

11. Tumor that is accessible to biopsy and patient is willing to undergone mandatory tumor biopsies at pre-treatment and on-treatment (unless exception granted by study PI)

12. Life expectancy ≥12 weeks as judged by treating physician

5.2 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.

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

5. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
6. Life-threatening illness unrelated to cancer.

7. Patients with uncontrolled coagulopathy or bleeding disorder.

8. Known hepatitis B surface antigen seropositive or known or suspected active hepatitis C infection
   Note: Patients who have isolated positive hepatitis B core antibody (ie, 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.

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

10. Known cardiopulmonary disease defined as:

    - Unstable angina;

    - Congestive heart failure (New York Heart Association [NYHA] Class III or IV; see appendix 3);

    - Myocardial infarction (MI) within 6 months prior to first dose (patients who had ischemic heart disease such as a (ACS), MI, and/or revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll);

    - Symptomatic Cardiomyopathy;

    - Clinically significant arrhythmia:

        1. History of polymorphic ventricular fibrillation or torsade de pointes,

2. Permanent atrial fibrillation [a fib], defined as continuous a fib for ≥ 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, within 6 months of starting protocol therapy, defined as symptomatic and incompletely controlled medically, 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.

- Clinically significant pulmonary hypertension requiring pharmacologic therapy.

11. Uncontrolled high blood pressure (ie, systolic blood pressure ≥ 160 mm Hg, diastolic blood pressure ≥ 100 mm Hg).

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

13. Left ventricular ejection fraction (LVEF) < 50% as assessed by echocardiogram or radionuclide angiography.

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

15. Known central nervous system (CNS) involvement unless controlled with surgery or radiation therapy and has demonstrated no progression over 3 months from last local modality therapy.

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

17. Female patients who are both lactating and breastfeeding or have a positive serum pregnancy test during the screening period or a positive urine pregnancy test on Day 1 before first dose of study drug.

18. 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).

19. 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).

20. Known hypersensitivity to a study agent(s).

21. Residual adverse events from prior therapy (other than endocrinopathies or alopecia or neuropathy due to chemotherapy) that have not resolved to Grade 0-1

22. Serious adverse immune related adverse events (grade 3 or 4) with previous immune checkpoint therapy, that were symptomatic and required prolong immunosuppression (>6weeks).

6. STUDY DRUG

6.1 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented prior to drug administration. Study drug will be administered only to eligible patients underthe supervision of the investigator or identified subinvestigator(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 BSA. BSA will be calculated using a standard formula (see example in Appendix 2) 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 than the dose should be adjusted according to this new body weight.

Pevonedistat will be administered roughly over 60-minute via IV infuision on Days 1, 3 and 5 of a 21 day cycle. Dose administered will be determined by patient's assigned dose escalation level, as outlined in the study design. Detailed instructions on drug preparation, handling and administration are outlined in section 6.8.

On Day 1 of each cycle, when the patient receives both agents, pembrolizumab will be administered following pevonedistat infusion. Patient should be monitored for adverse reactions roughly 30 minutes prior to infusion of the second agent.

Pembrolizumab 200 mg will be administered as an IV infusion over roughly 30 minutes on Day 1 of each cycle. The current label for pembrolizumab contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

6.2 Definitions of Dose Limiting Toxicity

DLT will be defined as any of the following events that are considered by the investigator to be related (possible, probably or definitely related) to therapy with pevonedistat and or pembrolizumab, and occur during the first 21 days of study therapy:

- Grade 3 or greater PT or aPTT elevation in the absence of anticoagulation therapy.
- Grade 2 or greater elevation of the PT or aPTT that is associated with clinically significant bleeding (CNS, GI, etc).
- Grade 3 or greater nausea and/or emesis despite use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-hydroxytryptamine 3 serotonin receptor antagonist given in standard doses and according to standard schedules.
- Grade 3 or greater diarrhea that occurs despite maximal supportive therapy
- Grade 3 arthralgia/myalgia despite the use of optimal analgesia
- Any other Grade 3 or greater non-hematologic toxicity with the following exceptions:
    - Brief (< 1 week) Grade 3 fatigue
    - Grade 3 hypophosphatemia
- Grade 3 or greater elevation in transaminases concurrent with Grade 2 or greater bilirubin
- Other pevonedistat-related non-hematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require a dose reduction or discontinuation of therapy with pevonedistat.
    - A delay in the initiation of Cycle 2 due to a lack of adequate recovery from treatment-related toxicity (recovery to ≤Grade 1 or to patient's baseline values):
        - Of more than 4 weeks due to hematologic toxicity
        - Of more than 2 weeks due to nonhematologic toxicities.
- Grade 4 neutropenia (ANC < 500 cells/mm^3) lasting more than 7 consecutive days
- Grade 3 neutropenia with fever and/or infection, where fever is defined as an oral temperature ≥ 38.5°C
- Grade 4 thrombocytopenia (platelets < 25,000/mm^3 but > 10,000/mm^3) lasting more than 7 consecutive days
- Grade 3 thrombocytopenia with bleeding
- A platelet count < 10,000/mm^3 at any time
- Grade ≥ 3 immune colitis
- Grade ≥3 immune pneumonitis

- Grade ≥ 3 immune hypophysitis
- Grade ≥ 3 Type I Diabetes Mellitus
- Grade ≥ 3 immune nephritis
- Grade 4 immune skin rashes (including, but not limited to SJS; TEN)
- Grade ≥3 of any other clinically significant immune mediated dose limitingtoxicities, including but not limited to: Guillain Barrè syndrome, myasthenia gravis, vasculitis, pancreatitis,encephalitis, myelitis and myocarditis.
- Grade 5 toxicity.

Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment will necessarily influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment related toxicities.

The incidence of DLTs occurring during Cycle 1 will represent the 21-day DLT period. This will be used to define the dose escalation and the RP2D. Study adverse events (AEs) will be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

6.3Dose-Modification Guidelines

Pevonedistat dose may be reduced by one or two dose levels based on type and grade of toxicity experienced. Guidelines for dose-modification to manage various toxicities are specified in sections 6.3.2 and 6.3.3.

Dose levels will not be reduced for pembrolizumab. Dose-modifications to manage immune-related toxicities and infusion related reactions attributed to pembrolizumab are detailed in sections 6.3.4 and 6.3.5, respectively

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 5.0).

Immunological AEs are expected to be related to pembrolizumab and should be managed as listed for pembrolizumab dose-modification, while non-immunologic toxicities are expected to be related to pevonedistat and should be managed as listed for pevonedistat. If a clinician is uncertain the attribution than dose modification of both agents for a toxicity can be done.

If one drug is discontinued due to toxicity the patient may continue on study with the other study drug.

6.3.1 Criteria for Retreatment and Dose Delays

6.3.1.1 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.

If dosing is interrupted within a cycle because of drug-related toxicity, and if the Principal investigator 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 (eg, 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 Principal investigator (or designee).

6.3.1.2 Initiation of a New Cycle

Treatment with study drugs will be repeated 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~~ Principal investigator. The maximum delay from end of a cycle to the initiation of a new cycle is 6weeks. Patients requiring a delay of longer, should be removed from the study unless there is a clear clinical benefit and this can be discussed with the principal 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 non-hematologic toxicity. An exception to this treatment plan is for a patient who experiences an immune related toxicity to pembrolizumab and pembrolizumab is held while that toxicity is managed. In this situation the patient may continue on cycle with pevonedistat alone until it is safe to treat with pembrolizumab again.

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 Principal investigator) will trigger a dose reduction if treatment resumes. The pevonedistat dose should be reduced by at least 1 dose level.

6.3.2 Pevonedistat 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.

6.3.3 Pevonedistat dose Modifications for Nonhematologic Toxicities

Pevonedistat Dose Adjustment Based on Serum Transminases and Total Bilirubin

ALT, AST and bilirubin grading will be determined by CTCAE version 5.0 in times per ULN irrespective of baseline levels.

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

For elevated LFTs of Grade 2 or 3 that occur on or after Cycle 1 Day 3, pevonedistat should be held; once the elevated AST or ALT returns to ≤Grade 1, and/or elevated bilirubin returns to ≤1.5×ULN or the patient's baseline level, pevonedistat dose may be resumed. For pevonedistat, a minimum of 1 full calendar day between any 2 doses should be maintained, and a maximum of 3 doses of pevonedistat within the cycle must not be exceeded.

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

Pevonedistat Dose Adjustment Based on Hypophosphatemia

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

Pevonedistat Dose Adjustment for Other Toxicities

For other ≥Grade 2 nonhematologic toxicities potentially related to pevonedistat, the pevonedistat dose may be reduced at the discretion of the Principal 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.

6.3.4 Pembrolizumab Dose Modifications for Management of Immune-Related Toxicities

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than on body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 1.

Table 2. Dose modification and toxicity management guidelines for immune-related AEs associated with pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv 5.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging
	Grade 3 or 4, or recurrent	Permanently discontinue		

	Grade 2			and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (i.e., diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (i.e., peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	

Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (e.g., propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (e.g., levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent	Permanently discontinue		

	Grade 3			
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

6.3.5 Pembrolizumab Dose Modifications for Management of Infusion-Reactions

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in Table 2.

Table 3. Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment**	Participant may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Participant is permanently discontinued from further study drug treatment.**	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

6.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Table 4. Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	For patients in the dose-escalation phase of a clinical study, agents such as acetaminophen and acetaminophen-containing products should not be administered 24 hours before, on the day of, and 24 hours after dosing with pevonedistat. For patients not in dose escalation, agents such as acetaminophen and acetaminophen-containing compounds may be used judiciously and should not exceed a dose of 2 g of acetaminophen in a 24 hour period.
Any investigational agent other than pevonedistat	For example androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate] are excluded.

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

6.5 Permitted Concomitant Medications and Procedures

Table 5. Concomitant Medications and Procedures 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. Growth factors may be used in specific circumstances after discussion with the PI. Use of growth factors may also be used in patients with Grade 3 or Grade 4 febrile neutropenia after discussion and agreement with the project clinician or designee. Additionally to avoid dose delays, patients who experience Grade 4 neutropenia (ANC <500/μL) with or without fever may receive granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF)
Platelet transfusion	Permitted as medically necessary per institutional guidelines (eg, for platelets <10,000/μL in the absence of clinical bleeding); see Section 6.9
Red blood cell transfusion	To be considered for all patients with anemia, especially those with hemoglobin values ≤8 g/dL.

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

6.6 Precautions and Restrictions

Pregnancy

It is not known what effects pevonedistat has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner.

Nonsterilized female patients of reproductive age group and male patients should use highly effective methods of contraception (see Appendix 5) through defined periods during and after study treatment as specified below.

- Female patients must meet 1 of the following:
- Postmenopausal (See Appendix 4) for at least 1 year before the Screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 1 highly effective method and 1 additional effective (barrier) method of contraception, at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug, or
- Agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. (Periodic abstinence [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).

6.7 Management of Clinical Events

Hemodynamic Compromise in Patients Receiving Pevonedistat

It is essential that the patients receiving pevonedistat are carefully evaluated at Screening and before each pevonedistat dose for early symptoms and signs of hemodynamic compromise and/or active infection. Particular attention should be paid to unexplained fever, tachycardia, hypotension, orthostasis, tachypnea, recent nausea and vomiting, and clinical evidence of dehydration. Patients who experience an untoward reaction with pevonedistat should be followed closely on subsequent dosing.

For patients for whom there is a concern of dehydration, the following guidance for rehydration before pevonedistat dosing may be considered: 500 mL/hour of 0.5 N saline given over 2 to 4 hours for a total of 1 to 2 L of fluid as clinically appropriate.

For all patients with anemia, and especially for those with hemoglobin values <8 g/dL at Screening or during the conduct of the study, RBC transfusions should be considered before pevonedistat dosing based on the risk of inadequate oxygenation, underlying cardiopulmonary status, clinical judgment, and/or hospital guidelines. Note: Transfusions should occur the day before doses given that pevonedistat is extensively distributed in RBCs.

Patients who experience signs and symptoms of hemodynamic compromise after pevonedistat dosing (eg, tachycardia, hypotension, orthostasis, changes in mental status, syncope, and dizziness) should be followed closely and managed with supportive care, including hospitalization, as clinically indicated.

Guidance for 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.

6.8 Description of Investigational Agents

6.8.1 Pevonedistat

Section redacted

<Pembrolizumab

Standard of care supply of pembrolizumab will be utilized for the study.

6.8.2 Preparation, Reconstitution, and Dispensing

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 vials must be kept in the original carton while equilibrating to room temperature. 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 or 0.9% saline solution, and then gently inverted repeatedly to mix. The pevonedistat prepared IV bag must be used within 6 hours (time to the end of an injection) if stored at ambient temperature. Alternatively, the prepared IV bag is chemically stable and may be stored for up to 18 hours at 2°C to 8°C. After 18 hours of storage at 2°C to 8°C, the prepared IV bag must be used within 3 hours (time to the end of an injection) upon coming to ambient temperature**.**

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

Preparation, Reconstitution and Dispensing for pembrolizumab will be based on standard guidelines for the agent.

6.8.3 Packaging and Labeling

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

Pembrolizumab drug supply will be labeled in accordance with current regulatory requirements

6.8.4 Storage, Handling, and Accountability

Vials of pevonedistat (TAK-924/MLN4924) are to be stored at 2°C to 8°C. Pevonedistat injection is stable at ambient temperature for 6 hours before dilution. All investigational supplies are to be kept in a secure area with controlled access.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The amount of drug to be administered will be based on body surface area (BSA). BSA will be calculated using a standard nomogram on Cycle 1, Day 1 (see Appendix 2), and at subsequent visits if the patient experiences a > 5% change in body weight from the weight used for the most recent BSA calculation.

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

All patients will receive pevonedistat diluted with 5% dextrose or 0.9% saline solution 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.

Standard guidelines for storage, handling and administration of pembrolizumab will be applicable for this study.

6.9 Study Compliance

Study drug will be administered or dispensed only to eligible patients under the supervision of the principal investigator. The appropriate study personnel will maintain records of study drug receipt and dispensing. When appropriate, study drug will be destroyed per institutional policy.

6.10 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:

- Adverse event

- Protocol violation
- Lost to follow-up
- Confirmed progressive disease using iRECIST v1.1
- Subsequent anti-cancer therapy
- Withdrawal by subject
- Study terminated
- Other

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed.

7. STATISTICAL AND QUANTITATIVE ANALYSES

7.1.1 Determination of Sample Size

This clinical trial will be a single-arm, non-randomized, open-label two stage phase I/II study of pembrolizumab and pevonedistat in dMMR/MSI-H cancers.With a null hypothesis of ≤3% response rate and an alternative hypothesis response rate of 20% with we can use Bayesian optimal phase II (BOP2) design: 1st stage 11 pts, if 1 or more responses, add 11 more. Among 22 patients, 34 or more responses are regarding promising. This controls type I error 5%, power 81%.

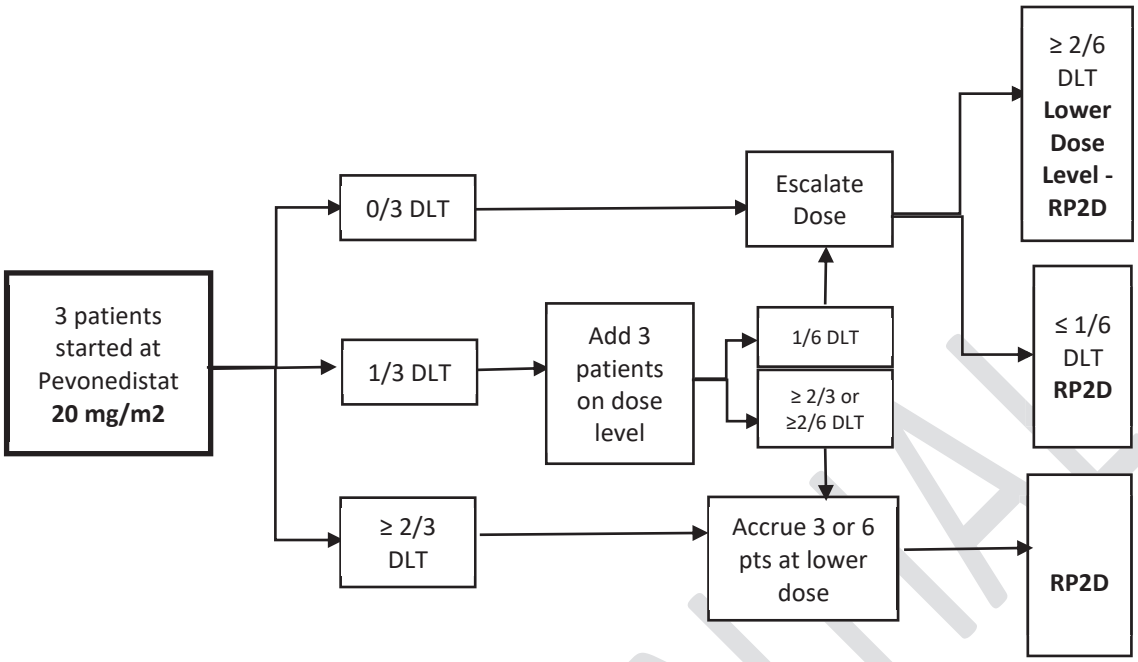
7.1.2 Safety Analysis

Descriptive analysis of toxicity will occur. Continuous monitoring will occur as listed below in toxicity monitoring.

7.1.2.1. Toxicity Monitoring

Phase I - Escalation Portion:

In order to provide RP2D, we plan to enroll on a 3+3 design with approximately 3-6 patients per cohort followed by a phase II two stage design in which 11 to 21 patients will be enrolled. Approximately 14-39 patients will be enrolled overall in the study to evaluate initial efficacy estimate of the proposed drug combination.



Phase II – Two Stage Portion:

Based on prior studies [29, 30], total treatment-related grade 3/4 toxicity rate of 15% and 17% may be assumed for pevonedistat and pembrolizumab, respectively. Based on these prior published data if toxicities are additive then a grade 3/4 rate for these two agents would be approximately 32%.

Toxicity monitoring will be implemented using the BOP2 design for possible/probable/ definitive treatement-related grade >= 3 AE. We will apply the toxicity monitoring rule in cohort sizes of 6, starting from the 6th patient, as indicated in Table 6 over the first 42 days of treatment (two cycles). AEs unrelated to the study treatments will not be included in the safety decision making. Study monitoring will be done in DMI database at MD Anderson.

The stopping rule in Table 6 is obtained by maximizing Pr(claim that the treatment is safe | $p_{tox} = 0.2$), while controlling Pr(claim that the treatment is safe | $p_{tox} = 0.5$) = 0.197, (i.e., the null toxicity rate of 0.5 and the alternative toxicity rate of 0.2) based on the following Bayesian stopping rule: the treatment is deemed unacceptably toxic if

$$Pr(p_{tox} \leq 0.5|data) < \lambda \left(\frac{n}{N}\right)^{\alpha/3},$$

where, n is the interim sample size, N is the maximum sample size, and λ=0.68 and α=0.74 are design parameters optimized, assuming a vague prior Beta(0.5,0.5) for p_{tox} to make "go/no-go" decision.

Given this is a novel combination the study will also monitor for signs of severe toxicity in the first three patients. If two related grade 4 events or a related grade 5 event occurs in these first 3 patients than the study will be stopped and discussions between Takeda and MD

Anderson will occur regarding continuation of clinical trial enrollment with an amendment required for further enrollment.

Table 6. Optimized Stopping Boundaries

# patients treated	Stop if # toxicity >=
6	4
12	6
18	9
22	10

The operating characteristics for patient toxicity monitoring is illustrated in Table 6.

Table 7. Operating Characteristics for Toxicity Monitoring

Toxicity rate	Early stopping (%)	Claim acceptable (%)	Sample size
0.5	71.20	19.67	13.3
0.4	41.35	51.05	17.1
0.3	15.65	81.90	20.1
0.2	3.09	96.72	21.6

7.1.2.2 Efficacy and Safety Monitoring:

The Investigator is responsible for completing efficacy/toxicity summary reports and submitting them to the IND office Medical Affairs and Safety Group, for review and approval. These should be submitted as follows:

Phase I –Escalation:

Toxicity summary report: After the first 3 evaluable patients, complete cycle 1 (first 21 days) of study treatment, and every 3 evaluable patients thereafter, prior to changing dose levels or expanding to phase II.

Phase II - Expansion:

Efficacy/Toxicity summary report: After the first 6 evaluable patients, complete cycle 2 of study treatment, and every 6 patients thereafter, until enrollment is complete.

A copy of the summary report should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

7.1.3 Pharmacokinetics

Blood samples will be collected for PK studies at time points indicated in the study Schedule of Events (Appendix 6). Specific instructions for collections will be detailed in the Research Blood and Tissue Collection Manual.

Pharmacokinetic Measurements
Serial blood samples will be collected from each patient for the determination of pevonedistat plasma concentrations ~~at~~ the time points indicated below. The timing, but not the number, of PK blood samples may be changed if emerging data indicate that an alteration in the sampling scheme is needed to better characterize the PK of pevonedistat.

To ensure that the measurements are representative of plasma exposure, blood draws will be conducted in the arm opposite to a patient's IV infusion. If only a single arm is available, blood should be drawn as distal to the site of the IV infusion as feasible, and the site of the blood draw should be documented.

The exact date and time of each sample collection and the actual start and stop times of the infusion should be recorded accurately, and particular care should be given to recording blood sampling times that occur close to the infusion.

Pharmacokinetic Assay Method
Plasma samples will be analyzed for pevonedistat concentrations using a GLP-validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

Pharmacokinetic Analysis
Individual pevonedistat plasma concentration-time data will be analyzed using standard noncompartmental methods using WinNonlin software (Pharsight, CA). The following PK parameters of pevonedistat will be estimated Cmax, Tmax, AUC24, Vss and CL, and t1/2 and AUC∞ (as data permit). Individual values and descriptive statistics of pevonedistat plasma concentration-time data and PK parameters will be listed and tabulated by treatment/ study day. Individual and mean pevonedistat plasma concentration data will also be plotted over time per treatment/study day. As data permit, exploratory PK-PD relationships (e.g. C_{max} or AUC vs response) will be examined using a direct PD model such as the E_{max} or Sigmoid E_{max} model.

7.1.4 Translational Studies

Paired biopsies: Biopsies aid the effort to further the study's exploratory objectives.

Evaluation of patient tumors prior to and on treatment will elucidate the impact of study therapy on immune activity and the tumor microenvironment.

To analyze potential mechanisms of anti-PD1/pevonedistat combination therapy resistance/sensitivity, we will first test if baseline factors such as neoantigen burden, destabilizing mutation burden, immune microenvironment characteristics, or combination thereof are indicative of response. Next, we will also evaluate these same type of parameters, but instead comparing their relative changes between pre- and post- treatment biopsies.

Given the expected phase 2 sample size of approximately 22 patients and assuming 50% responders (defined as having a clinical benefit rate (PR + CR + SD)) and accounting for approximately 10% inevaluable samples (i.e., biopsy specimen with inadequate or insufficient tumor), a total of 20 assessable paired biopsies we will have 80% power to detect an effect size of 1.32 between responders and non-responders in the molecular changes, at the significance level of 0.05. For responders (or non-responders), we will 80% power to detect an effect size of 0.996 for pre-post molecular changes.

To identify genes and pathways differentially expressed between responders and non-responders, we will apply linear methods such as the Limma provided in R-package. The associated p-values will be corrected for multiple testing using the Benjamini Hochberg adjustment method, resulting in highly reliable identification of differentially expressed genes, even when sample size is small. Logistic regression will be used to assess if baseline, as well as pre-post change, of neoantigen burden, destabilizing mutation burden, immune microenvironment characteristics, or combination thereof are indicative of response. Given the small sample size, the regression analysis will largely univariate with the possibility of multivariate with 2 or 3 predictors, when data allow

Optimally we plan to obtain at least 5 tissue cores from the core needled biopsies but the number of cores obtained will be affected by the patient clinical condition at the time of biopsy and determined by the radiologist who is performing the procedure. Core biopsy is typically performed using 21-18 gauge needle and with condition permitting, up to 5 cores should be collected. For full processing of biopsies please see laboratory manual

Blood and microbiome: Blood and stool samples will be obtained to evaluate stool microbiome change over time and blood will evaluate potential changes in ctDNA and immunological parameters over time. Blood analysis may include plasma analysis for markers including, but not limited to, interleukin (IL)-1α, IL-1β, IL-2, IL-5, IL-6, IL-8, IL-13, TNF-α, MCP, MIP-1β, G-CSF, GM-CSF, interferon-γ via a cytokine assay (for example Meso Scale Discovery, 40 Plex). Leukocyte subpopulations and immune activation status will be assessed on peripheral blood mononuclear cells.

For each subject, objective response will be determined per iRECIST v1.1, progression-free survival, duration of response, and overall survival will be calculated. Progression-free survival (PFS) is defined as the number of days from treatment start to the date of documented progression of disease/death and will be calculated for all patients. The overall

survival (OS) is defined as the time from treatment start until death or last follow-up. The duration of response is defined as the time from response until progression or last follow-up. The distribution of time-to-event endpoints including OS and PFS will be estimated using the method of Kaplan and Meier. Comparisons of time-to-event endpoints by important subgroups will be made using the log-rank tests. The association between response and patient's clinical characteristics will be examined by Wilcoxon's rank sum test or Fisher's exact test, as appropriate. The pre- and on treatment difference regarding microbiome and tumor biopsy will be compared using Wilcoxon signed-rank test.

8. ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a medicinal product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

8.1.1.1 Adverse Event Attribution

Attribution is the determination of whether an adverse event is related to a medical treatment or procedure.

Definite - the adverse event is clearly related to the investigational agent(s).

Probable - the adverse event is likely related to the investigational agent(s).

Possible - the adverse event may be related to the investigational agent(s).

Unlikely - The adverse event is doubtfully related to the investigational agent(s).

Unrelated - The adverse event is clearly NOT related to the investigational agent(s).

8.1.1.2 Adverse Event Severity The severity of the adverse events (AEs) will be graded according to the U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute, Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0.

Events not included in the NCI CTCAE will be scored as follows:

Grade 1: Mild: discomfort present with no disruption of daily activity, no treatment required beyond prophylaxis.

Grade 2: Moderate: discomfort present with some disruption of daily activity, require treatment.

Grade 3: Severe: discomfort that interrupts normal daily activity, not responding to first line treatment.

Grade 4: Life Threatening: discomfort that represents immediate risk of death

The investigator (or physician designee) isresponsible for verifying and providing source documentation for all adverse events, assigning the attribution and assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution for all adverse events for subjects enrolled.

All participants will be registered in the Clinical Oncology Research System (CORe)

8.1.1.3 Adverse Event Recording

Adverse Events will be recorded in the electronic database [_____] following the NCI recommended Adverse Event Recording Guidelines table below. The phase I guidelines will

be followed during the Phase I portion of the trial, and the guidelines for phase II studies, for the Phase II portion.

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

8.1.2 Serious Adverse Events

8.1.2.1 Serious Adverse Event (SAE) Reporting Requirements for M D Anderson Sponsor Single Site IND Protocols

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the followingoutcomes:Death

A life-threatening adverse event

Inpatient hospitalization or prolongation of existing hospitalization

A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.

A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy on Reporting Adverse Events for Drugs and Devices".

Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent.

Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

All SAEs, expected or unexpected/ initial or follow up, must be reported to the IND Office within 5 working days of knowledge of the event regardless of the attribution.

Death or life-threatening events that are unexpected, possibly, probably or definitely related to drug must be reported (initial or follow up) to the IND Office within 24 hours of knowledge of the event

Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

The electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MD Anderson IRB.

All events reported to the supporting company must also be reported to the IND Office

Reporting to FDA:

Serious adverse events will be forwarded to FDA by the IND Sponsor according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

8.1.2.2 Serious Adverse Events Reporting to the Supporting Company

Serious AE (SAE) means any untoward medical occurrence that at any dose:

- Results in **death.**
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (see clarification in the paragraph below on planned hospitalizations).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

8.1.2.3 Procedures for Reporting Serious Adverse Events

Adverse Events 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.

Adverse Events which are **serious** must be reported to Millennium Pharmacovigilance (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 follow-up period that the Principal-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness (es).

Since this is an investigator-initiated study, the principal investigator Michael Overman, MD, also referred to as the Principal-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor~~– investigator's EC~~ or IRB.

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

Fatal and Life Threatening SAEs within 24 hours of the Principal-investigator's observation or awareness of the event

All other serious (non-fatal/non life threatening) events within 4 calendar days of the Principal-investigator's observation or awareness of the event

The SAE report must include at minimum:

- **Event term(s)**
- **Serious criteria**
- **Intensity of the event(s):** Principal-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- **Causality of the event(s):** Principal-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 Millennium Pharmacovigilance (or designee).

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 Principal-investigator, including the MDACC SAE reporting form.

8.2 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 Principal-investigator must fax a completed Pregnancy Form to the Millennium Pharmacovigilance or designee immediately (see Section 8.2). The pregnancy must be followed for the final pregnancy outcome (i.e., delivery, still birth, miscarriage) and Millennium Pharmacovigilance or designee will request this information from the Principal-investigator.

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

Suggested Pregnancy Reporting Form:
Pregnancy Report Form (a sample will be provided)

9. ADMINISTRATIVE REQUIREMENTS

9.1 Product Complaints

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

For Product Complaints, call
Phone 1-844-ONC-TKDA (1-844-662-8532)
Email: GlobalOncologyMedinfo@takeda.com
Fax: 1-800-881-6092, Hours Mon-Fri, 9 a.m.- 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, anthe MDACC SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 8.2).

10. REFERENCES

The list of references will be molecule specific for each template and should be generated using EndNote. See a member of the Medical Writing department for assistance with this.

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11.

Contact Medical Writing for standard/typical appendices (e.g., response criteria, example formula for calculation of body surface area). Teams should verify that the appendix items are current (source information should be included).

Appendix 1: Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Table 8. 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.[31]

Appendix 2: Body Surface Area

Body surface area (BSA) will be calculated using the standard formula that is used for all patients within the MD Anderson Electronic healthcare record, EPIC.

Appendix 3: New York Heart Association Classification of Cardiac Disease

The following table presents the New York Heart Association (NYHA) classification of cardiac disease [32].

Table 9. NYHA Classification of Cardiac Disease

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

Appendix 4: 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 (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

Appendix 5: 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.
5) 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 methods.

Appendix 6: Schedule of Events

Table 10. Schedule of Events

	Screening (-28 Days to D1)	Treatment Cycle (21 Days)[c]														End of Treatment (EOT) [d]	Long-term OS follow-up (every 3-6 months after EOT) by phone
		Cycle 1					Cycle 2			Cycle 3			Cycle 4 (Restaging)				
	Days	1	3	5	8	15	1	3	5	1	3	5	1	3	5		
Study Procedures																	
Inclusion/ Exclusion Criteria	X																
Demo-graphics and Medical History	X																
Prior and Concomitant Medication Review (to be captured in medical record)	X	X					X			X			X			X	
Written Informed Consent	X																
Pevonedistat[a]		X	X	X			rs	X	X	X	X	X	X	X	X		
Pembrolizumab[a]		X					X			X			X				

Repeat steps from cycles 2-4 for subsequent cycles until PD

HIV, HBV, HCV antibody testing	X																
Serum or urine pregnancy test[e]	X	X															
Physical examination[a]	X	X					X			X			X			X	
Vital signs[a,f]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	
ECOG PS[a]	X	X														X	
Toxicity Assessment[a]	X	X					X			X			X			X	
12-lead ECG and ECHO or MUGA[g]	X																
Coagulation[b]	X																
Free T4, TSH[a]	X						X (only Cycle 2)						X			X	
Complete chemistry panel[a, h]	X	X		X			X			X			X			X	
Complete blood count/ Hematology[a, i]	X	X	X	X	X	X	X			X			X			X	
Select chemistry panel[a, j]			X	X	X	X		X	X		X	X		X	X		

Urinalysis [(a)]	X																
Correlative blood collection[(a)]		X					X (only Cycle 2)						X (only cycle 4 + 7)			X (preferrably may be done at time of progression)	
PK blood collection (only cycles 1-3)[k]																	
Microbiome collection[(a)] (only screening and cycle 4)	X												X				
Tumor Imaging Evaluation (+/- 10 day window)	X												X				
Biopsy (+/-7 days for on-tx biopsy)	X						X										

[a:] +/-4 day window period is permitted from D1 of each cycle for study drug administration and protocol related procedures (other than imaging + biopsy). +/-1 day for day 3 and 5 though strong preference to keep on scheduled days. +/-2days for day 8 and 15. Also days 8 and 15 of cycle 1 labs can be done locally

[b:] Coagulation panel includes PT and aPTT

[c:] On dosing days, all procedures are to be performed prior to administration of study drug(s), unless otherwise specified.

[d:] End of treatment visit will occur 30 days (+10 days) after last dose of study drug(s) or prior to start of subsequent antineoplastic therapy, if that occurs sooner. Can be done virtually, though in person preferred.

[e:] only mandatory for women of child bearing potential

[f:] patient vitals are to be obtained at screening, on listed days of each cycle, at end of treatment visit and as clinically indicated. Height at screening only, weight on day 1 of each cycle

[g:] ECG to be performed as clinically indicated during treatment

[h]:includes albumin, blood urea nitrogen, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, phosphorus, sodium, urate, direct bilirubin, total bilirubin and protein, and liver enzymes (ALP, AST, ALT, LDH) . Before each dose of pevonedistat infusion ALP, ALT, AST and total bilirubin assessments must be done and results reviewed by a treating physician.

[i]:add white blood count differential along with other standard components

[j]:The select chemistry panel will include the following: BUN, creatinine, phosphate, total bilirubin, albumin, ALP, AST, and ALT. Before each dose of pevonedistat infusion ALP, ALT, AST and total bilirubin assessments must be done and if abnormal results reviewed by a treating physician or advanced practice provider. Treatment parameters will be present on treatment orders to ensure notification on abnormal values occurs.

[k]:PK sampling time points are specified in Table 11

[l]Imaging should be standard of care imaging for that tumor type. In general this should be CT scans or MRI scans.

Table 11. PK sampling timepoints

	Cycle 1						**Cycle 2**	**Cycle 3**
	Day 1	**Day 2**	**Day 3**	**Day 5**	**Day 6**	**Day 7**	**Day 1**	**Day 1**
Phase 1	X	X	X	X	X	X	X	X
Sampling Timepoints[a]	Pre-dose[b], EOI, 0.5, 1, 2, 3,4, 8 hours post dose	24 hours post dose	48 hours post dose	Pre-dose[b], EOI, 0.5, 1, 2, 3,4, 8 hours post dose	24 hours post dose	48 hours post dose	EOI, 1 hour post dose	EOI, 1 hour post dose
Pase II	X			X			X	X
Sampling Timepoints[a]	Pre-dose[b], EOI, 1, 3 hours post dose			Pre-dose[b], EOI, 1, 3 hours post dose			EOI, 1 hour post dose	EOI, 1 hour post dose

[a] Unless specified, all time points refer to end pevonedistat infusion; [b] Within one hour prior to study drug administration.
EOI: End of infusion. Times are approximate, though goal should be to obtain sample within +/-10min for each post-dose timepoint.

Appendix 7: Laboratory Manual

Please refer to the related Research Blood and Tissue Collection Manual for details on various biospecimen collection processes for this protocol.