Title: A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [14C]-Pevonedistat in Patients with Advanced Solid Tumors

NCT Number: NCT03057366

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STATISTICAL ANALYSIS PLAN

STUDY NUMBER: Pevonedistat-1013

A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [^{14}C]-Pevonedistat in Patients with Advanced Solid Tumors

PHASE 1

Version**:** Final

Date**:** 19 March 2018

Prepared by:

Personal Protected Data

Based on:

Protocol Version: Final

Protocol Date: 29 November 2016

1.1 Approval Signatures

Study Title: A Phase 1 Study to Assess Mass Balance, Pharmacokinetics, and Metabolism of [^{14}C]-Pevonedistat in Patients with Advanced Solid Tumors

Approvals:

Personal Protected Data	Date
Personal Protected Data	Date
Personal Protected Data	Date
Personal Protected Data	Date
Personal Protected Data	Date

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT FIGURES

3.0 LIST OF ABBREVIATIONS

ADME	absorption, distribution, metabolism, excretion
AE	adverse event
$Ae_{feces,}{}^{14}C$	cumulative amount of [14C]-radioactivity excreted in the feces up to the last sampling interval
$Ae_{feces,}{}^{14}C_{,t1-t2}$	amount of [^{14}C]-radioactivity excreted in feces in a sampling interval
$Ae_{total,}{}^{14}C_{\ total}$	cumulative excretion of [^{14}C]-radioactivity from the body ($Ae_{total,}{}^{14}C= Ae_{urine,}{}^{14}C + Ae_{feces,}{}^{14}C$)
Ae_{urine}	cumulative amount of drug excreted in urine
$Ae_{urine,}{}^{14}C$	cumulative amount of [^{14}C]-radioactivity excreted in the urine up to the last sampling interval
$Ae_{urine,}{}^{14}C_{,\ t1-t2}$	amount of [^{14}C]-radioactivity excreted in urine in a sampling interval
ALL	acute lymphoblastic leukemia
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AML	acute myeloid leukemia
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{∞}	AUC from time zero to infinity, calculated using the observed value of the last quantifiable concentration
AUC_{last}	AUC from time zero to time of the last quantifiable concentration
AUC_{t}	AUC from time zero to time t
AUC_{τ}	AUC during a dosing interval
BID	twice daily
BSA	body surface area
CDL	cullin-dependent ubiquitin E3 ligases
CFR	Code of Federal Regulations
CLR	renal clearance
Cmax	maximum observed concentration
CR	complete response
CRO	contract research organization
CT	computed tomography
CV	coefficient of variation
CYP	cytochrome P450
DCSI	development core safety information
DDI	drug-drug interaction
DME	drug-metabolizing enzyme
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form

EOS	End-of-Study
FDA (US)	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GI	gastrointestinal
HIV	human immunodeficiency virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IEC	independent ethics committee
IRB	institutional review board
IV	Intravenous(ly)
MDS	myelodysplastic syndrome
Millennium	Millennium Pharmaceuticals, Inc
pevonedistat	research name of pevonedistat hydrochloride; TAK-924
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NAE	NEDD8-activating enzyme
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	non-small cell lung cancer
PD	progressive disease
PK	pharmacokinetics
PR	partial response
QTc	rate-corrected QT interval
RECIST	Response in Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SC	subcutaneous(ly)
SmPC	Summary of Product Characteristics
SoC	standard of care
$t_{1/2z}$	terminal disposition phase half-life
TEAE	treatment-emergent adverse event
t_{max}	time of first occurrence of Cmax
TRA	total radioactivity
ULN	upper limit of the normal range
US	United States
USP	United States Pharmacopeia

4.0 OBJECTIVES

4.1 Primary Objectives

The primary objectives are as follows:

- To assess the mass balance (ie, cumulative excretion of total radioactivity [TRA] in urine and feces) of pevonedistat following a single 1-hour infusion of 25 mg/m^2 [^{14}C]-pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA in patients with advanced solid tumors in Part A.
- To characterize the PK of pevonedistat in whole blood, plasma, and urine, and of TRA in plasma and whole blood following a single 1-hour infusion of 25 mg/ m^2 [^{14}C]- pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA in patients with advanced solid tumors in Part A.

4.2 Secondary Objectives

The secondary objectives are as follows:

- To collect samples for characterization of the metabolic profile of pevonedistat in plasma, urine, and feces following a single 1-hour infusion of 25 mg/m^2 [^{14}C]-pevonedistat IV solution containing approximately 60 to 85 μCi (approximately 2.22-3.145 MBq) of TRA (maximum dose of 50 mg) in patients with advanced solid tumors in Part A.
- To evaluate the safety and tolerability of pevonedistat in patients with advanced solid tumors after a single dose in Part A and in combination with either docetaxel or carboplatin+paclitaxel in Part B.
- To evaluate disease response that may be observed with the combination of pevonedistat and docetaxel or pevonedistat and carboplatin+paclitaxel in patients with advanced solid tumors (Part B).

4.3 Study Design

This is a 2-part, open-label, multicenter, mass balance and ADME study in adult patients with advanced solid tumors. It is expected that approximately 4 to 6 PK-evaluable patients will be enrolled in this study. Once enrolled into the study, patients will be administered a single dose of [^{14}C]-pevonedistat via IV infusion.

4.3.1 Part A: Mass Balance/ADME Assessment

Part A represents the period for assessment of the mass balance, PK, metabolism, and elimination of pevonedistat in this population.

Patients who meet all inclusion criteria and no exclusion criteria will be admitted to the Part A study site on the morning of Day -1 for predose assessments and to begin confinement. On the morning of Day 1, patients will receive a single dose of 25 mg/ m^2 (equivalent to approximately 43 mg for a typical individual of 1.73 m^2 BSA, with a maximum absolute dose of up to 50 mg)

[^{14}C]-pevonedistat IV solution (containing approximately 60-85 µCi [approximately 2.22-3.145 MBq] of TRA) via a 1-hour infusion. The actual amount of administered radioactivity will be documented for each patient.

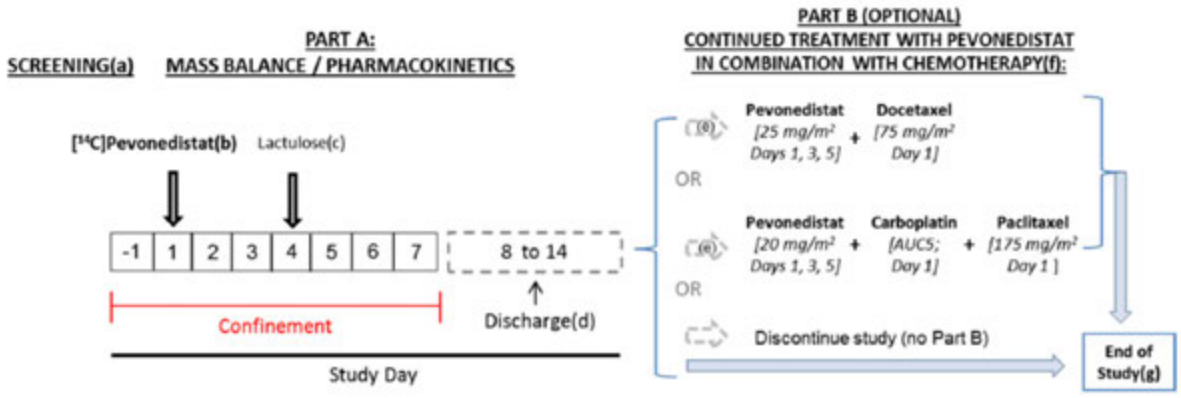
Patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met(see protocol section 9.5.17), with a maximum estimated confinement period of 9 to 14 days.

4.3.2 Part B: Continued Treatment With Pevonedistat in Combination With Chemotherapy (OPTIONAL)

After completion of the mass balance/ADME assessment portion of the study, patients will have the opportunity to continue into Part B at a secondary study site, which can begin within approximately 2 weeks of the patient completing Part A (ie, when the patient has met the Part A discharge criteria; see Protocol Section 9.5.17). Participation in Part B is optional. Any patient who continues on to Part B will need to be re-evaluated for entry criteria before treatment in Part B can begin. Patients will receive pevonedistat in combination with either docetaxel or carboplatin+paclitaxel as recommended by the investigator. Pevonedistat will be administered on Days 1, 3, and 5 at the dose of 25 mg/ m^2 in combination with docetaxel 75 mg/ m^2 on Day 1 every 3 weeks, or pevonedistat on Days 1, 3, and 5 at the dose of 20 mg/ m^2 in combination with carboplatin AUC5+paclitaxel 175 mg/ m^2 on Day 1 every 3 weeks. Safety and disease assessments will be conducted in Part B of the study. Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03, effective date 14 June 2010

For more details on Study design, refer to Study Protocol section 6.0. Figure 4.a below provides an overview of the study design of Parts A and B.

Figure 4.a Study Overview



(a) Screening assessments will be performed within 28 days before administration of [^{14}C]-pevonedistat.
(b) On the morning of Day 1, following the collection of Day 1 predose assessments, patients will receive a single dose of 25 mg/ m^2 (equivalent to approximately 43 mg for a typical individual of 1.73 m^2 BSA up to a maximum absolute dose of 50 mg) [^{14}C]-pevonedistat IV solution (containing approximately 60-85 µCi [approximately 2.22-3.145 MBq] of TRA) via a 1-hour infusion.
(c) Two 15 mL doses of oral lactulose will be administered, separated by approximately 2 hours, on the evening of Day 4; the second dose of lactulose will be withheld if the first dose was not tolerated. Lactulose may also be administered as needed.
(d) During Part A, patients will be required to stay at the Part A study site for approximately 8 days or until the discharge criteria are met, with a maximum estimated confinement period of 9 to 14 days.
(e) Eligible patients may continue into Part B (optional), which can begin within approximately 2 weeks of the patient completing Part A (ie, when the patient has met the discharge criteria). Cycle length is 21 days. Treatment assignment in Part B will be based on recommendation by the investigator.
(f) The maximum duration of treatment will be 12 cycles; however, if it is determined after discussion between the investigator and the sponsor that a patient would derive benefit from continued treatment, the patient may remain on the current combination therapy or receive pevonedistat as a single agent beyond 12 cycles.
(g) Patients will attend an EOS visit 30 days (+10 days) (safety follow-up) after the last dose of study drug or before the start of subsequent therapy for their indication, if that occurs sooner.

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoints

The primary endpoints are as follows:

- Summary statistics of PK parameters of pevonedistat and TRA in plasma and whole blood: C_{max}, time of first occurrence of C_{max} (t_{max}), and AUC from time zero to time of the last quantifiable concentration (AUC_{last}).
- Cumulative percentage of urinary recovery, percentage of fecal excretion, and percentage of TRA in urine and feces over the entire period of collection.
- Summary statistics of PK parameters of pevonedistat in urine: cumulative amount excreted in urine (Ae_{urine} and percentage of dose) and renal clearance (CLR).

5.2 Secondary Endpoints

The secondary endpoints are as follows:

- Safety parameters: AEs, SAEs, and abnormal laboratory values reported.
- Metabolite profiles in plasma, urine, and feces.
- Measures of disease response based on investigators assessment using the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (Version 1.1).

5.3 Exploratory Endpoint

[redacted]

6.0 DETERMINATION OF SAMPLE SIZE

The sample size for this study is not based on statistical considerations.

On the basis of the ALARA principle (As Low [radioactive burden] As Reasonably Achievable) set forth in the 96/29/EURATOM directive, a sample size of 4 to 6 PK-evaluable patients is considered sufficient to provide adequate characterization of the mass balance, PK, and metabolism of pevonedistat in patients with cancer. Patients will be replaced if they are not evaluable for PK.

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

In general, summary tabulations will include the number of observations, (arithmetic) mean, standard deviation (SD), geometric mean and coefficient of variation (%CV) for PK related parameters, median, minimum, and maximum for continuous variables, and the number and percent (of non missing) per category for categorical data, unless specified otherwise. Means and medians will be presented to 1 more decimal place than the recorded data. The standard deviations (SDs) will be presented to 2 more decimal places than the recorded data. Confidence intervals about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Descriptive statistics will be presented with the same precision as the original data. The PK parameters will be summarized with a precision of 3 significant digits, while t_{max} is presented with the number of relevant decimal places to specify the sampling time. Percent CV and frequency percentages will be presented as integers.

Summary statistics will be calculated by time point, if applicable.

All confidence intervals, statistical tests, and resulting P-values will be reported as 2-sided and will be assessed at α=0.05 significance level unless otherwise stated. P-values will be rounded to 3 decimal places prior to assessment of statistical significance.

Screen failure subjects will be grouped and listed at the end.

7.1.1 Study Definitions

A Patient is considered to be enrolled when the first dose of study drug has been administered. Study start date is defined as the date of first dose of study drug for part A.

7.1.2 Definition of Study Days

Study Day 1 is defined as the date on which a subject is administered their first dose of the study drug. Other study days are defined relative to the Study Day 1 with Day 1 being Study Day 1 and Day -1 being the day prior to Study Day 1.

7.1.3 Definition of Baseline Values

Part A

Unless otherwise specified, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration during Part A. For analysis of ECG data, the baseline value is the average of the screening and Part A Day 1 predose value if ECG is collected at both of the screening and Part A Day 1 predose. If ECG is collected at only one of these two time points, the baseline value takes the value of the one which is collected.

Part B

Similarly, the baseline value is defined as the value collected at the time closest to, but prior to, the start of study drug administration during Part B. Since there is no screening visit for Part B, the baseline value for ECG is also the one collected at the time closest to, but prior to, the start of study drug administration during Part B.

7.1.4 Windowing of Visits

All data will be categorized based on the scheduled visit at which they were collected. The analysis of PK data and determination of PK parameters will be based on the actual elapsed time post dose relative to the first dosing.

7.1.5 Withdrawals, Dropouts, Loss to Follow-up

Patients who are not PK-evaluable will be replaced. Generally no additional patients will be enrolled due to withdrawals, dropouts, or loss to follow-up.

7.1.6 Imputations for Missing Dates

Dates of initial diagnosis, prior therapy, surgery or radiation which are partially missing will be imputed as follows:

- If the date has a month and year but the day is missing, the 15th will be inserted as the day.
- If the date has a year but the month and the day are missing, June 30th will be inserted.

7.1.6.1 Analysis of Missing Adverse Event Dates

- If the start date has month and year but day is missing, the event will be considered
  - treatment emergent for Part A if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of study drug in Part A, and on or before the month and year of the date of the last dose of study drugs in Part A plus 30 days for patients who do not continue into Part B or the date of the first dose of study drugs in Part B for patients who continue into Part B.
  - treatment emergent for Part B if both the month and year of the start date of the event are on or after the month and year of the date of the first dose of study drugs in Part B, and on or before the month and year of the date of the last dose of study drugs in Part B plus 30 days.
- If the start date has year, but day and month are missing, the event will be considered
  - treatment emergent for Part A if the year of the start date of the event is on or after the year of the date of the first dose of pevonedistat in Part A, and on or before the year of the date of the last dose of study drugs in Part A plus 30 days for patients who do not continue into Part B or the date of the first dose of study drugs in Part B for patients who continue into Part B.

  - treatment emergent for Part B if the year of the start date of the event are on or after the year of the date of the first dose of study drugs in Part B, and on or before the year of the date of the last dose of study drugs in Part B plus 30 days.

- If the start date of an event is completely missing, the event will be considered
  - treatment emergent for Part A for patients who do not continue into Part B
  - treatment emergent for Part A for patients who continue into Part B if the ending date of the event is before the date of the first dose of study drugs in Part B
  - treatment emergent for both Part A and Part B for patients who continue into Part B if the ending date does not reflect whether the AE ends prior to the first dose of study drug in Part B.

7.2 Randomization and Stratification

No randomization or stratification will be performed in this study.

7.3 Unblinding

As this is an open-label study, no unblinding methodology is required.

7.4 Statistical Software

SAS version 9.1 (or higher) will be used for all analyses.

7.5 Analysis Sets

7.5.1 Safety Analysis Set

The safety analysis set for Part A is defined as all enrolled patients who receive at least 1 dose of [^{14}C]-pevonedistat during Part A. All safety analyses in Part A will be performed using the safety population for Part A.

The safety population for Part B is defined as all patients who continue to Part B and receive at least 1 dose of study drugs administered during Part B. All safety analyses in Part B will be performed using the safety population for Part B.

7.5.2 Pharmacokinetic (PK)-Evaluable Population

The PK-evaluable population is defined as a) all enrolled patients who receive the protocol-specified single [^{14}C]-pevonedistat dose in Part A, b)did not receive any excluded medications throughout the completion of Part A, and c) have sufficient concentration-time data to permit reliable estimation of PK parameters and mass balance. The patients to be included in the PK-evaluable population will be determined by the Takeda Clinical Pharmacologist upon review of the final data.

PK and mass balance analyses during Part A will be performed using the PK-evaluable population.

7.5.3 Response-Evaluable Population

The response-evaluable population is defined as all patients who receive at least 1 dose of study drug in Part B, have measurable disease as entry criteria for Part B, and have at least 1 post-baseline disease assessment.

Response analyses for Part B will be performed using the response-evaluable population.

7.6 Disposition of Subjects

7.6.1 Patient Disposition

Separate tabulations of patient disposition data will be generated for Part A and Part B.

A tabulation of patient disposition data for Part A will include the number of patients for the following categories: patients treated (safety population for Part A), patients in the PK-evaluable population, patients completing Part A, patients who discontinued study treatment during Part A (including the washout period), the primary reason off study treatment (including the washout period). Patients will be considered to have completed Part A if they have completed the protocol-specified assessments within Part A of the protocol. Percentages will be based on the number of patients in the safety populations for Part A.

A tabulation of patient disposition data by treatment arm and the Part B total for Part B will also be generated to included the following categories: patients treated (safety population for Part B), patients in the response-evaluable population, patients completing Part B, patients who discontinue study treatment from Part B, and the primary reason off study treatment. Patients will be considered to have completed Part B of the study if they have completed 12 cycles of treatment or discontinue treatment during Part B for any of the following reasons:

- Adverse event.
- Lost to follow-up.
- Progressive disease.
- Protocol violation.
- Study terminated by sponsor.
- Symptomatic deterioration.
- Unsatisfactory therapeutic response.
- Withdrawal by subject.
- Other (to be specified)

Percentages in the table of disposition data for Part B will be based on the number of patients in the safety populations for Part B

Data concerning patient disposition (eg, primary reason off study treatment, patient population) will be presented in by-patient listings.

7.7 Demographic and Other Baseline Characteristics

7.7.1 Demographics

Demographics will be summarized for the total safety population in Part A, and by treatment arm and total for the safety population in Part B. Demographic data to be evaluated will include age at screening, sex, ethnicity, race, height, weight and body surface area (BSA).

BSA is calculated for each patient using the following formula:

$$\mathbf{BSA} = \sqrt{\frac{Height(cm) \times Weight(kg)}{3600}}$$

Both Part A and Part B use Height collected at screening. Part A uses weight collected at screening. If a weight at screening is not available, the Part A Day 1 pre-dose weight can be used. Part B uses weight collected at the visit closest, but prior to the Part B Cycle 1 Day 1 study drug administration.

No inferential statistics will be generated.

7.7.2 Baseline Disease Characteristics

Baseline disease characteristics (disease type, disease stage, sites of involvement, time since initial diagnosis) will be listed for the safety population in Part A, and by treatment arm and total for the safety population in Part B. ECOG performance status will be listed similarly in the same table.

Information on prior therapies will be summarized for the safety population in Part A, and by treatment arm and total for the safety population in Part B. Summarized information on prior therapies will include:

- Number of patients with prior chemotherapy.
- Months from last dose of prior chemotherapy to first dose.
- Number of patients with prior radiation.
- Months from last prior radiation to first dose.
- Number of patients with prior surgery or non-radiation procedures.
- Number of patient with prior transplant.

Missing dates will be imputed as described in section 7.1.6.

In addition, prior chemotherapy regimens will be tabulated by treatment arm and total in Part B. List and categorization of prior chemotherapy regimens is described in Appendix 1.

7.7.3 Inclusion/Exclusion Criteria

All inclusion/exclusion information on enrolled patients will be included in by-patient listings. Eligibility criteria for dosing during Part B for patients who continue into Part B will be

presented in a separate listing. These listings will include whether all criteria were satisfied. For patients who did not satisfy the criteria, the criteria number will be listed with the deviation.

In addition, all protocol deviations will be reviewed, identified and listed by Part A and Part B. Any enrolled patients who did not meet inclusion or met exclusion criteria will be listed under the category "Not meeting study inclusion/exclusion criteria".

7.7.4 Medical History

Patients with a medical (and/or surgical) history will be presented in a by-patient listing, including the medical and surgical history, date of onset and the outcome status (whether it is resolved or ongoing).

7.7.5 Concomitant Medications

All concomitant medications will be mapped to generic terms according to the World Health Organization (WHO) drug dictionary. The number and percentage of patients taking concomitant medications will be tabulated by WHO drug generic term, presented for the safety population in Part A, and by treatment arm and total for the safety population in Part B. Patients are counted once for each WHO drug generic term. Concomitant procedures will not be coded.

Concomitant medication for Part A is defined as any medication that occurs after administration of the first dose of study treatment during Part A and up through 30 days after the last dose of study drug during Part A for patients who do not continue into Part B or up through Part B C1D1 (pre-dose) for patients who continue into Part B.

Concomitant medication for Part B is defined as any medication that occurs after administration of the first dose of study treatment during Part B and up through 30 days after the last dose of study drug during Part B.

Concomitant therapies with start or end dates that are completely or partially missing will be analyzed using the same imputation rules as adverse events.

Concomitant medications and procedures will be presented in separate by-patient listings.

7.8 Study Drug Exposure and Compliance

7.8.1 Extent of Exposure

<u>PART A:</u>

The listing of Exposure to study drug for part A will be provided. The listing will contain the start and end times of infusion, Expected Dose, Actual dose administered, any dose interruptions and reason for dose interruptions

<u>Part B</u>

The extent of exposure will be based on the number of cycles received and the mean number of doses administered per cycle. The distribution of the number of cycles received will be presented by treatment arm for all patients treated in Part B. Patients will be considered to have been

treated for a cycle if they receive at least one dose of study drug during the 21 days of that cycle. Percentages will be calculated by treatment arm, and total for Part B.

For Pevonedistat, calculation of Percent Dosing Intensity will use for Daily Expected Dose (mg), Daily Prepared Dose (mg), and Daily Dose Received (mg). Daily Expected Dose and Daily Prepared Dose may differ if there are dose decreases.

Total Dose Received, Total Dose Expected, and Dosing Intensity during Part B will be based on the following formulas:

$$\text{Total Dose Received} = \text{Sum of Daily Dose Received on all days with Pevonedistat administration in Part B}$$

$$\text{Total Dose Expected} = \text{Daily Expected Dose} * 3 \text{ doses per cycle} * \text{number of treated cycles}$$

$$\text{Percent Dosing Intensity} = \frac{\text{Total Dose Received}}{\text{Total Dose Expected}} * 100$$

For chemotherapy, Daily Expected Dose, Total Dose Received, Total Dose Expected, and Dosing Intensity for each standard of care drug will be based on the following formulas:

$$\text{Daily Expected Dose (Docetaxel and Paclitaxel)} = \text{Dose Level Assigned at Study Entry (mg/m}^2\text{)} * \text{Body Surface Area (m}^2\text{)}$$

$$\text{Daily Expected Dose (Carboplatin)} = \text{Dose Level Assigned AUC at Study Entry (mg x min/mL)} * (\text{Glomerular filtration rate (mL/min)} + 25)$$

$$\text{Daily Prepared Dose (Docetaxel and Paclitaxel)} = \text{Scheduled Dose Level (mg/m}^2\text{)} * \text{Body Surface Area (m}^2\text{)}$$

$$\text{Daily Prepared Dose (Carboplatin) (mg)} = \text{Scheduled Dose Level (AUC)} * (\text{Glomerular filtration rate} + 25)$$

$$\text{Daily Dose Received} = \text{Daily Prepared Dose} * \left(\frac{\text{Volume of IV bag actually infused (mL)}}{\text{Prepared Volume}} \right)$$

AUC is the area under the free carboplatin plasma concentration versus time curve.

7.8.2 Treatment Compliance and Modifications

The actions on study drugs (Dose Held, Dose Reduced, Dose Interrupted, Dose Delayed, Dose Missed, Dose Increased, or Discontinued) will be summarized by treatment arm and total in Part B. For Part B, data will be summarized for Cycle 1 only as well as all cycles. A patient will count only once for each type of action.

7.9 Efficacy Analyses (Part B)

Efficacy analysis is only conducted for Part B, where efficacy is not a primary endpoint. A summary of the best overall response as determined by the investigator using the RECIST version 1.1 guidelines will be presented as a measure of disease response of pevonedistat in combination with chemotherapy. The number and percentage of patients in each disease response category (eg, complete response [CR], partial response [PR], stable disease [SD], and progressive disease [PD]) will be presented by treatment arm. Percentages will also be calculated

for the total in Part B. All evaluations of response will be conducted using the response-evaluable population.

The duration of disease response (CR or PR) will be presented in a by-patient listing for responders. Duration of response is the time from the date of first documented response per the investigator response assessment to the date of first documentation of PD, or the date of last disease assessment if the patient has no documentation of PD. The duration of response (in months), will be summarized descriptively by treatment arm for responders.

The duration of SD or better will be presented in a by-patient listing for all response-evaluable patients. Duration of SD or better is the time from the date of first dose to the date of first documentation of PD, or the date of last disease assessment if the patient has no documentation of PD. The duration of SD or better (in months) and the number of cycles with SD or better will also be summarized descriptively by treatment arm for all response-evaluable patients.

Results from all disease response assessments and whether there was symptomatic deterioration will be presented in by-patient listings.

Any tumor assessments after the alternate antineoplastic therapies or after disease progression will be excluded in the analyses.

7.10 Pharmacokinetic/ Pharmacogenomic Analysis

7.10.1 Pharmacokinetic Analysis

The PK-evaluable population will be used for the description of the concentration-time profiles, and for the estimation of pevonedistat and total radioactivity PK parameters.

PK parameter analysis will be based on concentrations of total radioactivity and pevonedistat in whole blood, plasma, urine and feces. Mass balance (% dose recovered) will be derived based on the total radioactivity, in urine, and feces.Whole blood, plasma, urine and feces will be collected at pre-specified times prior to and following study drug administration. Actual specimen collection times will be used for the calculation of PK and mass balance parameters. In the event that actual collection times are either unreliable or missing, scheduled collection times will be used. Both scheduled and actual collection times will be presented in listings. Concentrations of pevonedistat that are below the limit of quantification (BLQ) will be treated as zero. Concentration data that are considered anomalous may be excluded from concentration summaries and plots and will not be used in the calculation of PK parameters. Evidence or explanations will be provided to justify the exclusion of data.

When summarizing concentrations, PK parameters, or mass balance, a minimum of 2 patients are required to show the arithmetic mean and geometric mean, and at least 3 patients are required to show the standard deviation and coefficient of variation (CV).

7.10.2 PK and Mass Balance Parameters

The following PK and total radioactivity (TRA) parameters will be computed by noncompartmental methods, as data permit, and tabulated for each subject:

- *TRA in plasma and whole blood:*

C_{max}	Maximum observed total radioactivity	ng-eq
t_{max}	First time at which C_{max} occurs	hr
AUC_{last}	Area under the total radioactivity-time curve from time 0 to the time of the last quantifiable measurement, estimated using the linear-log trapezoidal rule	hr*ng-eq (TRA)
$t_{1/2z}$	Terminal disposition phase half-life	hr
AUC_{∞}	Area under the total radioactivity-time curve from time 0 to infinite time	hr*ng-eq

- *TRA in urine:*

$Ae_{urine,}\ ^{14}C_{,t1-t2}$	Amount of [^{14}C]-radioactivity excreted into urine per sampling interval	ng-eq
$Fe_{urine,}\ ^{14}C_{,t1-t2}$	Fraction of administered [^{14}C]-radioactivity excreted in urine per sampling interval	%
$Ae_{urine,}\ ^{14}C$	Cumulative amount of [^{14}C]-radioactivity excreted into urine up to the last sampling interval	ng-eq
$Fe_{urine,}\ ^{14}C$	Cumulative fraction of administered [^{14}C]-radioactivity excreted in urine	%

- *TRA in feces:*

$Ae_{feces,}\ ^{14}C_{,t1-t2}$	Amount of [^{14}C]-radioactivity excreted into feces per sampling interval	ng-eq
$Fe_{feces,}\ ^{14}C_{,t1-t2}$	Fraction of administered [^{14}C]-radioactivity excreted in feces per sampling interval	%
$Ae_{feces,}\ ^{14}C$	Cumulative amount of [^{14}C]-radioactivity excreted into feces up to the last sampling interval	ng-eq
$Fe_{feces,}\ ^{14}C$	Cumulative fraction of the administered [^{14}C]-radioactivity excreted in feces	%

- *Total cumulative excretion of TRA:*

$Ae_{total,}\ ^{14}C$	Total cumulative excretion of [^{14}C]-radioactivity excreted in urine and feces $Ae_{total,}\ ^{14}C = Ae_{urine,}\ ^{14}C + Ae_{feces,}\ ^{14}C$	ng-eq
$Fe_{total,}\ ^{14}C$	Cumulative fraction of administered [^{14}C]-radioactivity excreted in urine and feces $Fe_{total,}\ ^{14}C = Fe_{urine,}\ ^{14}C + Fe_{feces,}\ ^{14}C$	%

- *pevonedistat in whole blood and plasma:*

C_{max}	Maximum observed pevonedistat concentration	ng/mL
T_{max}	First time at which C_{max} occurs	hr
AUC_{last}	Area under the concentration-time curve from time 0 to the time of the last quantifiable measurement, estimated using the linear-log trapezoidal rule	hr*ng/mL
$t_{1/2z}$	Terminal disposition phase half-life	hr
AUC_{∞}	Area under the concentration-time curve from time 0 to infinite time	hr*ng/mL
CL	Clearance	L/hr

- *pevonedistat in urine (per sampling interval and total):*

Ae_{urine}	Amount of pevonedistat excreted unchanged in urine	µg
Cumulative Ae_{urine}	Cumulative amount of pevonedistat excreted unchanged in urine	µg
Fe_{urine}	Fraction of the administered dose excreted unchanged in urine	%
Cumulative Fe_{urine}	Cumulative fraction of the administered dose excreted unchanged in urine	%
CL_R	Renal clearance	L/hr

Individual patient plasma and urine pevonedistat parameter data will be listed. Individual patient TRA (mass balance) parameter data will be listed. Descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, CV, median, minimum, and maximum) will be used to summarize individual parameter data.

7.10.3 PK and TRA Profiles

Individual patient whole blood, plasma and urine pevonedistat concentration-time data will be listed. Whole blood, plasma, urine, and fecal TRA-time data will be listed for each patient. Both scheduled and actual collection times will be presented in listings.

Descriptive statistics (N, arithmetic mean, standard deviation, geometric mean, CV, median, minimum, and maximum) will be used to summarize pevonedistat concentration and TRA versus time data in Part A of the study.

Mean (SD) cumulative percentage of dose recovered in urine, feces, and combined urine and feces will be plotted.

Mean concentration-time profiles will be plotted. Radioactivity (plasma and whole blood) and pevonedistat (plasma and whole blood) concentration-time profiles will be presented. There will be two presentations of this plot: linear scale, and semi-logarithmic scale (ie, logarithmic concentration scale). Individual concentration-time profiles will also be plotted. Radioactivity (plasma and whole blood) and pevonedistat (plasma and whole blood) concentration-time profiles will be presented on both a linear and a semi-logarithmic scale. Planned specimen collection times will be used in all plots. In linear plots, a value of zero will be substituted for any BLQ values. In semi-logarithmic plots, BLQ values will be treated as missing.

7.11 Safety Analysis

Safety analyses will be conducted separately for Part A and Part B.

Safety evaluations will be based on the incidence, severity, type of AEs, clinically significant changes or abnormalities in the patient's physical examination, vital signs, ECG, and clinical laboratory results.

These analyses for Part A will be performed using the safety population for Part A. Safety analyses for Part B will be performed by treatment arm using the safety population for Part B defined in section 7.5.1.

7.11.1 Adverse Events

AEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA).

A treatment-emergent AE for Part A is defined as any AE that occurs after administration of the first dose of study treatment during Part A and up through 30 days after the last dose of study drug during Part A for patients who do not continue into Part B or up through Part B C1D1 (pre-dose) for patients who continue into Part B.

A treatment-emergent AE for Part B is defined as any AE that occurs after administration of the first dose of study treatment during Part B and up through 30 days after the last dose of study drug during Part B.

AEs will be tabulated by system organ class (SOC), high level term (HLT), and preferred term (PT). Summary tabulations include the following subsets:

- Treatment-emergent AEs.
- Drug-related treatment-emergent AEs.
- Grade 3 or higher treatment-emergent AEs.
- Grade 3 or higher drug-related treatment-emergent AEs.
- Treatment-emergent AEs resulting in study drug discontinuation.
- SAEs.
- Treatment-emergent drug-related SAEs.

Most commonly reported (at least 10% of all patients) treatment-emergent AEs will be presented by preferred term.

Adverse events with start dates that are completely or partially missing will be analyzed as described in section 7.5.1:

7.11.2 Overall Summary

The number of patients who experience any of the following treatment emergent adverse events will be summarized.

- Any adverse event.
- Grade 3 or higher adverse event.
- Drug-related adverse event.
- Drug-related Grade 3 or higher adverse event.
- Serious adverse event.
- Drug related serious adverse event.
- Adverse events resulting in study drug discontinuation.
- On-study deaths.

Percentages will be calculated for the Part A total, arm totals for Part B and the Part B total.

7.11.3 Serious Adverse Events

The number and percentageof patients experiencing at least one treatment emergent serious AE (SAE) will be summarized by MedDRA SOC, HLT, and PT. Similar summary will be generated for treatment emergent drug-related SAEs.

By-patient listings of the SAEs will be presented (the patient listing will contain all SAEs regardless of treatment emergent AE status). The drug-related SAEs will also be presented.

7.11.4 Deaths

By-subject listings of the deaths will be presented. All deaths occurring on-study will be displayed (regardless of treatment emergent AE status). On-study death is defined as the death that occurs between the first dose of study drug and 30 days after the last dose of study drug.

7.11.5 Adverse Events Resulting in Discontinuation of Study Drug

The number and percentage of patients experiencing at least one adverse event resulting in discontinuation of study drug will be summarized by MedDRA SOC, HLT, and PT.

By-patient listing of AEs resulting in discontinuation of study drug will be presented. All AEs resulting in discontinuation of study drug occurring on-study will be displayed (regardless of treatment emergent AE status).

7.11.6 Adverse Events Resulting in Dose Reduction

The number and percent of patients experiencing at least one adverse event resulting in dose reduction will be summarized by MedDRA MedDRA SOC, HLT, and PT.

A by-patient listing of AEs resulting in dose reduction of study drug will be presented. All AEs resulting in dose reduction of study drug occurring on-study will be displayed.

7.11.7 Adverse Events Resulting in Dose Modification

The number and percent of patients experiencing at least one adverse event resulting in dose modification (including dose Reduction, Delay or Permanent Discontinuation) will be summarized by MedDRA SOC, HLT, and PT.

A by-patient listing of AEs resulting in dose modification of study drug will be presented. All AEs resulting in dose reduction of study drug occurring on-study will be displayed.

7.11.8 Clinical Laboratory Evaluations

For the purposes of summarization, all laboratory values will be converted to standardized units. If a lab value is reported using a non-numeric qualifier (eg, less than (<) a certain value, or greater than (>) a certain value), the given numeric value will be used in the summarization, ignoring the non-numeric qualifier.

If a subject has repeated laboratory values for a given time point, the value from the last evaluation will be used.

Shift tables of the change in NCI CTCAE (v4.03: June 14, 2010) from baseline to the post baseline worst CTCAE grade will be generated. If necessary, graphical displays will be used to show changes in laboratory measures over time for each individual patient; 1) line graphs of individual tests over time for each patient; and 2) scatter plots of baseline versus worst post-baseline values.

In addition, the lines of mean and median estimates over time may be graphed for a selected list of test parameters. The box plots of creatinine and platelet may be graphed too. By patient listings of desired lab parameters may be generated, if deemed necessary. For complete list of lab analytes, see Appendix 2.

7.11.9 Vital Signs

Graphical displays will be used to show changes in vital sign parameters, including oral temperature, heart rate, and systolic and diastolic blood pressure, over time.

Change from baseline and by-patient listing will also be presented.

7.11.10 12-Lead ECGs

Echocardiogram results (eg, LVEF) will be presented in by-patient listings separately for Part A and Part B.

7.11.11 Eastern Cooperative Oncology Group (ECOG) Performance Status

ECOG shifts from baseline to post-baseline assessment over time will be tabulated for Part B.

7.12 Interim Analysis

No interim analysis is planned.

7.13 Changes in the Statistical Analysis Plan

Reference materials for this statistical plan include Clinical Study Protocol Pevonedistat-1013 (dated 29 November 2016), and the accompanying data collection documents (Annotated Case Report Form [CRF], version 1.0 and 2.0 dated 09 March 2017).

8.0 REFERENCES

9.0 APPENDICES

9.1 Appendix 1

Prior Chemotherapy Regimens Categories:

Taxane-containing regimens	BEVACIZUMAB+CARBOPLATIN+PACLITAXEL BEVACIZUMAB+CISPLATIN+DOCETAXEL BEVACIZUMAB+CISPLATIN+PACLITAXEL BEVACIZUMAB+PACLITAXEL CAPECITABINE+DOCETAXEL CAPECITABINE+PACLITAXEL CARBOPLATIN+PACLITAXEL CARBOPLATIN+PACLITAXEL+TRASTUZUMAB CISPLATIN+DOCETAXEL CISPLATIN+DOCETAXEL+FLUOROURACIL CISPLATIN+PACLITAXEL CYCLOPHOSPHAMIDE+DOCETAXEL CYCLOPHOSPHAMIDE+DOCETAXEL+DOXORUBICIN CYCLOPHOSPHAMIDE+DOXORUBICIN+PACLITAXEL DOCETAXEL (TAXOTERE) DOCETAXEL+DOXORUBICIN DOCETAXEL+FLUOROURACIL DOXORUBICIN+PACLITAXEL FLUOROURACIL+PACLITAXEL GEMCITABINE+PACLITAXEL PACLITAXEL (ABRAXANE FOR INJECTABLE SUSPENSION; APO-PACLITAXEL) PACLITAXEL+TRASTUZUMAB
Regimens containing a taxane but not a platinum	BEVACIZUMAB+PACLITAXEL CAPECITABINE+DOCETAXEL CAPECITABINE+PACLITAXEL CYCLOPHOSPHAMIDE+DOCETAXEL CYCLOPHOSPHAMIDE+DOCETAXEL+DOXORUBICIN CYCLOPHOSPHAMIDE+DOXORUBICIN+PACLITAXEL DOCETAXEL (TAXOTERE) DOCETAXEL+DOXORUBICIN DOCETAXEL+FLUOROURACIL DOXORUBICIN+PACLITAXEL FLUOROURACIL+PACLITAXEL GEMCITABINE+PACLITAXEL PACLITAXEL (ABRAXANE FOR INJECTABLE SUSPENSION; APO-PACLITAXEL) PACLITAXEL+TRASTUZUMAB
Regimens containing a platinum but not a taxane	CAPECITABINE+CISPLATIN CAPECITABINE+CISPLATIN+EPIRUBICIN CAPECITABINE+EPIRUBICIN+OXALIPLATIN CAPECITABINE+OXALIPLATIN CARBOPLATIN (PARAPLATIN-AQ) CARBOPLATIN+ETOPOSIDE CARBOPLATIN+FLUOROURACIL CETUXIMAB+CISPLATIN+VINBLASTINE

	CETUXIMAB+CISPLATIN+VINORELBINE CISPLATIN (PLATINOL) CISPLATIN+EPIRUBICIN+FLUOROURACIL CISPLATIN+ETOPOSIDE CISPLATIN+FLUOROURACIL CISPLATIN+FLUOROURACIL+LEUCOVORIN CALCIUM CISPLATIN+GEMCITABINE CISPLATIN+IRINOTECAN CISPLATIN+PEMETREXED CISPLATIN+VINBLASTINE FLUOROURACIL+LEUCOVORIN CALCIUM+OXALIPLATIN FLUOROURACIL+OXALIPLATIN OXALIPLATIN (ELOXATIN)
Regimens containing both a platinum and a taxane	BEVACIZUMAB+CARBOPLATIN+PACLITAXEL BEVACIZUMAB+CISPLATIN+DOCETAXEL BEVACIZUMAB+CISPLATIN+PACLITAXEL CARBOPLATIN+PACLITAXEL CARBOPLATIN+PACLITAXEL+TRASTUZUMAB CISPLATIN+DOCETAXEL CISPLATIN+DOCETAXEL+FLUOROURACIL CISPLATIN+PACLITAXEL

9.2 Appendix 2

Panel	Test
Chemistry	Albumin
	Alanine aminotransferase (SGPT)
	Aspartate aminotransferase (SGOT)
	Alkaline Phosphatase
	Carbon Dioxide
	Direct Bilirubin
	Total Bilirubin
	Blood urea nitrogen
	Blood urea nitrogen (mg/dL)/Creatinine (mg/dL)
	Calcium
	Chloride
	Creatinine
	Creatinine clearance
	Glomerular filtration rate (estimated)
	Glucose
	Gamma-glutamyl-transpeptidase
	Lactate dehydrogenase
	Magnesium
	Phosphate
	Potassium
	Sodium
	Urate
Hematology	Platelets
	Hematocrit
	Hemoglobin
	White Blood Cells
	Lymphocyte Count
	Neutrophils (ANC)
	Monocytes
	Eosinophils
	Basophils

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'UTC')
Personal Protected Data	Clinical Pharmacology Approval	20-Mar-2018 19:13 UTC
	Statistical Approval	20-Mar-2018 19:14 UTC
	Clinical Science Approval	20-Mar-2018 19:18 UTC
	Biostatistics Approval	20-Mar-2018 21:11 UTC
	Nonclinical Scientist Approval	20-Mar-2018 21:42 UTC