ECOG-ACRIN cancer research group
Reshaping the future of patient care

EA2187

A Phase 2 Study of Pevonedistat in Combination with Carboplatin and Paclitaxel in Advanced Intrahepatic Cholangiocarcinoma

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STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology
SWOG / SWOG

ACTIVATION DATE

January 31, 2020

Agents	IND#	NSC#	Supply
Pevonedistat	[redacted]	793435	NCI
Carboplatin	N/A	241240	Commercial
Paclitaxel	N/A	673089	Commercial

IND Sponsor: DCTD, NCI

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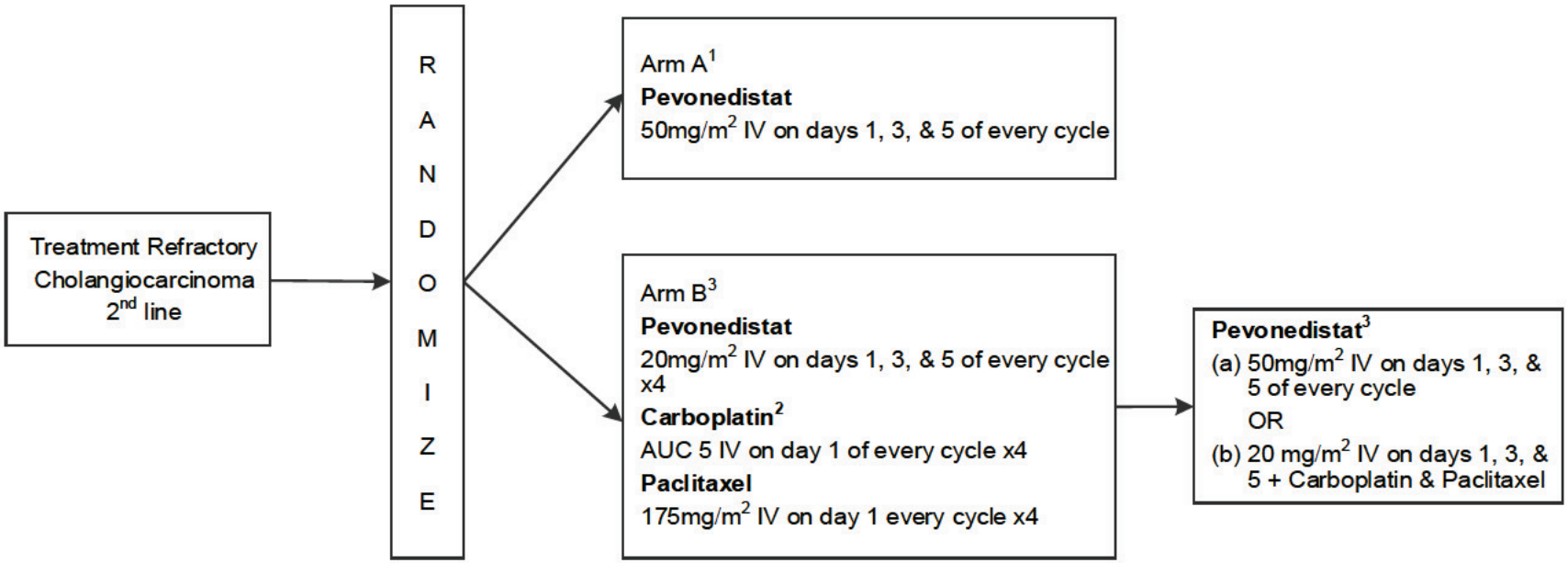
CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For study data submission:**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Cycle: 21 days
Accrual Goal: 52

1. For Arm A, treatment will continue until disease progression, unacceptable toxicity, or patient desire to discontinue study therapy.
2. Refer to section 5.1.2.2 for carboplatin dose specifics.
3. For Arm B at any time after 4 cycles of combination therapy, the treating physician is given discretion to continue combination therapy or switch to pevonedistat monotherapy. Treatment will continue on Arm B until disease progression, unacceptable toxicity or patient desire to discontinue study therapy.

1. Introduction

1.1 Cholangiocarcinoma Background

Cholangiocarcinoma is an uncommon malignancy that arises from the epithelial cells of bile ducts. Unfortunately, this disease has a very poor prognosis, with a five-year survival rate of 5-10%.[1] Most patients present with advanced disease, with only 10% presenting with resectable disease. Unfortunately, recurrence after resection remains high, with rates reported between 44% and 70% at 5 years.[2-4] The ABC-02 trial demonstrated the benefit of gemcitabine and cisplatin, which is now considered standard of care for first-line chemotherapy in fit patients.[5] Unfortunately, resistance to therapy ultimately develops. Outcomes are quite poor in the second-line setting with minimal anti-tumor activity seen with second line chemotherapy and no clear standard of care in this setting.[6] Recently, the ABC-06 trial demonstrated an overall survival benefit of FOLFOX (5-flurouracil, leucovorin, oxaliplatin) over best supportive care in the second line setting (HR 0.69; 95% CI 0.50-0.97; p=0.031).[7] The benefit seen in this trial was marginal, thus there is still a clear need to develop novel therapeutic strategies, enhancing the efficacy of cytotoxic chemotherapy regimens, and to investigate predictive biomarkers in cholangiocarcinoma.

1.2 Neddylation Pathway in Cholangiocarcinoma

The ubiquitin proteasome system (UPS) controls a broad array of cellular functions via protein degradation that mediate cell growth and survival, cellular signaling, and transcription factor regulation.[87] Ubiquitin (Ub) conjugation via covalent linkage to a protein tags it for degradation by a proteasome. Ubiquitylation is a multi-step process that transfers Ub to target substrates through an enzymatic cascade that involves three enzymes: Ub-activation (E1), Ub-conjugating (E2), and Ub-ligase (E3). A subgroup of E3 ligases include Cullin RING ligases (CRL) which are responsible for approximately 20% of cellular proteins labeled for degradation.[7] CRL substrates include regulators of cell cycle progression, apoptosis, DNA damage responses, and signaling transduction. This subgroup of E3 ligases are regulated via a Ub-like ligand, NEDD8 (neural precursor cell expressed, developmentally down-regulated 8), via covalent conjugation. As with Ub, neddylation to CRL occurs in three enzymatic steps that include NEDD8-activating enzyme (NAE), E2 conjugation (UBC12), and an E3 ligase. Given the downstream substrates of CRLs include a number of oncoproteins and tumor suppressors, inhibiting neddylation is an ideal oncologic therapeutic target.

Up-regulation of neddylation has been demonstrated in several malignancies including melanoma, NSCLC, and intrahepatic cholangiocarcinoma.[10-12] Pre-clinical work by Gao *et al* studied tumor samples from 322 patients with resected intrahepatic cholangiocarcinoma (ICC) and demonstrated that NEDD8 was overexpressed in malignant cells in 68.9% of cases. Notably surrounding normal intrahepatic bile duct cells showed weak or negative expression of NEDD8. Likewise, other players of neddylation including NAE1, UBA3, and UBC12 were also overexpressed.

To illustrate the clinical relevance of neddylation upregulation, the authors then grouped patients according to high or low expression of these markers. Univariate analyses demonstrated that upregulation of the neddylation pathway

correlated with higher rate of relapsed disease after resection. Patients with low expression of NEDD8 had a median time to recurrence of 44.0 months compared to 14.0 months in patients with high expression of NEDD8. Multivariate Cox analysis confirmed that co-expression of NEDD8 and NAE1 is an independent negative prognostic factor, with double the risk of recurrent disease following resection compared to low expression of NEDD8 and NAE1.

1.3 Pevonedistat

Pevonedistat (MLN4924) is an investigational adenosine sulfamate analogue that inhibits NAE by covalently forming a NEDD8 adduct. In this form, NAE is unable to process NEDD8 for CRL conjugation, thus inhibiting CRL activity and leading to accumulation of CRL substrates. Pevonedistat's anti-tumor activity is via primarily via induction of DNA damage, but also includes inducing autophagy and inhibition of NF-κB signaling.[13-20] Pevonedistat DNA-damage activity is via several mechanisms. Double-strand DNA break (DSB) repair is initiated by binding of the Ku heterodimer.[21] Neddylation is essential for the degradation of Ku and release of nonhomologous end-joining (NHEJ) core complex from DNA following repair. By serving as a barrier, persistence of this repair complex inhibits genome replication and promotes cell death. Additionally, inhibition of neddylation promotes DNA re-replication during S phase of the cell cycle due to stabilization of CDT1, leading to DNA damage.[9] Lastly, neddylation plays a regulatory role in inter-strand crosslinkage (ICL) repair. Neddylation is required for ATR/CHK1 activation and for subsequent FANCD2 monoubiquitination in the Fanconi anemia pathway.[16] Monoubiquinated FANCD2 is required for complete ICL repair including the activation of nucleotide excision repair, translesion synthesis, and recruitment of homologous recombination repair factors such as BRCA1, BRCA2, RAD51, and FAN1.

Pre-clinical data supports pevonedistat's activity against ICC. Gao *et al* demonstrated inhibited cell proliferation and inhibition of colony formation in a dose-dependent fashion in ICC cell lines, including 2 of 4 primary ICC cell lines.[10] Notably, one of the primary ICC cell lines with the lowest expression of NAE1 was resistant to treatment. Of the ICC cell lines that responded, pevonedistat induced G2 cell cycle arrest followed by apoptosis or senescence. Further analysis of protein levels demonstrate accumulation of known CRL substrates, including cell cycle regulators (WEE1), IκB-α (inhibitor of NF-κB), and CDT1 (regulator of DNA replication). Pevonedistat also induced DNA-damage response, confirmed by the elevation of phosphorylated H2AX and CHK1. Lastly, pevonedistat has anti-tumor activity in xenograft models. Tumor growth was inhibited in pevonedistat-treated cholangiocarcinoma compared to control tumors. Pevonedistat-treated xenograft tumors also demonstrated accumulation of CRL substrates and demonstrated a marked decrease in Ki-67 compared to controls.

1.4 Pevonedistat Single Agent Activity

The clinical development of pevonedistat started with four clinical trials with doses ranging from 25 to 278 mg/m^2.[22-25] In these studies, toxicity involving multiorgan 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 ≥ 110mg/m^2. Because of this, a revised risk mitigation strategy, including limiting the dose ≤100mg/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.

Pevonedistat has shown single-agent activity in patients with advanced solid tumors in two phase I clinical trials, at doses ranging from 25 to 209 mg/m^2.[22,23] One of the initial trials by Sarantopoulos *et al* studied pevonedistat monotherapy in patients with advanced, non-hematologic malignancies to determine the optimal dosing schedule.[23] This study included several gastrointestinal (GI) malignancies including colorectal, gastric, pancreatic, and esophageal cancers (n = 19). Though no objective responses were noted on study, 42% (n = 8) of patients remained on pevonedistat for ≥3 cycles (21 day cycle) demonstrating potential clinical activity in GI malignancies. The single agent recommended phase II dose (RP2D) is 50 mg/m^2 administered on days 1, 3, and 5 of 21-day cycle. Of note, pevonedistat has not been investigated as a single agent in subjects selected for neddylation pathway activation in their cancers or in any patients with cholangiocarcinoma.

1.5 Pevonedistat in Combination with Chemotherapy

Carboplatin is a platinum analogue chemotherapeutic agent that has been in use since the 1980s. Platinums function as alkylating agents by binding to cellular DNA to form interstrand crosslinks (ICL). Given pevonedistat's inhibition of ICL repair, there is clinical interest in combining therapy with carboplatin to enhance cytotoxic activity. Preclinical data has validated the chemosensitizing effect of pevonedistat combination with cross-linking cytotoxic agents including platinum chemotherapy, mitomycin C, and ionizing radiation.[10,21,26] In ICC cell lines, Gao *et al* validated the additive effect of cisplatin with pevonedistat.[10]

A phase Ib, multi-arm study (NCT01862328) has studied the safety of gemcitabine (1000 mg/m^2 days 1,8,15), docetaxel (75 mg/m^2 day 1), and carboplatin/paclitaxel (AUC 5 day 1 / 175 mg/m^2 day 1) in combination with pevonedistat in patients with solid tumors.[27] The gemcitabine plus pevonedistat arm was discontinued early due to toxicity (grade 3/4 febrile neutropenia (n = 2) and grade 3 transaminitis (n = 1)) and dose escalation was not pursued. Dose-limiting toxicities (DLTs) in the docetaxel arm were grade 3 AST/ALT elevated (n = 4) requiring dose hold and dose reduction, with a maximum tolerated dose (MTD) of pevonedistat 25 mg/m^2. DLTs in the carboplatin/paclitaxel plus pevonedistat arm included grade 3 febrile neutropenia (n = 1; 15 mg/m^2), grade 3 AST/ALT elevation (n = 3; 20 mg/m^2, n = 2; 25mg/m^2), and grade 4 thrombocytopenia (n = 1; 15 mg/m^2). One DLT of grade 3 AST elevation occurred during MTD expansion requiring dose reduction. The RP2D was determined to be pevonedistat 20 mg/m^2 on days 1, 3, and 5 in combination with carboplatin AUC 5 and paclitaxel 175 mg/m^2 of a 21-day cycle. Preliminary data suggest antitumor activity in patients with heavily pre-treated solid tumors. This includes two patients on study with cholangiocarcinoma. One patient with biphasic hepatocellular and cholangiocarcinoma was treated in the carboplatin/paclitaxel arm with a partial response on treatment for 8 cycles. The second patient with cholangiocarcinoma was treated on the docetaxel arm with a partial response, treated for 3 cycles. Overall, the combination was well tolerated with manageable toxicities. Of note all patients accrued in this trial had bilirubin at screening ≤ upper limits of normal. Safety of pevonedistat in patients with hepatic

impairment is currently being investigated. As of August 2019 no data is available on the exposure of pevonedistat in patients with hepatic impairment. Common adverse events of any grade include fatigue (57%), nausea (39%), anemia (33%), increased AST (30%), and increased ALT (27%).

1.6 Rationale for the Overall Study Design

Patients with cholangiocarcinoma have a poor prognosis. There is no clear standard of care systemic chemotherapy regimen in the second-line setting for patients with advanced disease. Therefore, we propose a randomized phase 2 study evaluating single agent pevonedistat (Arm A) and the combination of pevonedistat with carboplatin and paclitaxel (Arm B) for patients with unresectable cholangiocarcinoma in the second-line setting. Pevonedistat has never been studied as a single agent in cholangiocarcinoma, nor has it been studied in cancers over-expressing components of the neddylation pathway. In addition, given this safety data, preliminary activity, and rationale pevonedistat deserves further investigation with chemotherapy for cholangiocarcinoma. Carboplatin and paclitaxel was chosen as the chemotherapy regimen for this study as this has published safety data in combination with pevonedistat and there is a recommended phase 2 dose. Additionally, responses were seen with this combination in the phase I clinical trial, warranting further investigation.[28]

2. Objectives

2.1 Primary Endpoints

2.1.1 To determine the objective response rate of pevonedistat as a single agent and in combination with carboplatin and paclitaxel in patients with unresectable intrahepatic cholangiocarcinoma.

2.2 Secondary Endpoints

2.2.1 To evaluate the safety profile of pevonedistat alone and in combination with carboplatin and paclitaxel in patients with intrahepatic cholangiocarcinoma.

2.2.2 To determine the clinical benefit rate of patients with advanced ICC treated with pevonedistat monotherapy and in combination with carboplatin and paclitaxel.

2.2.3 To determine progression-free survival of patients treated with pevonedistat monotherapy and in combination with carboplatin and paclitaxel.

2.2.4 To determine overall survival of patients treated with pevonedistat monotherapy and in combination with carboplatin and paclitaxel.

2.3 Exploratory Endpoints

2.3.1 To determine whether overexpression of NEDD8, NAE1, and UBC12 predict response to treatment.

2.3.2 To identify the mutation profile of those cholangiocarcinomas with overexpression of the neddylation pathway.

2.3.3 To bank specimens for further future investigations.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Patient must be ≥ 18 years of age.

_____ 3.1.2 Patient must have an ECOG Performance Status 0-1.

_____ 3.1.3 Patient must have a life expectancy ≥ 12 weeks

_____ 3.1.4 Patient must have histologically confirmed intrahepatic cholangiocarcinoma or biphasic hepatocellular carcinoma and cholangiocarcinoma that is metastatic or unresectable and who have progressed on or been intolerant of one prior line of systemic gemcitabine containing chemotherapy regimen.

NOTE: Prior immunotherapy or targeted therapies are allowed and will not be considered a line of therapy unless administered with cytotoxic chemotherapy.

_____ 3.1.5 Patient must have measurable disease as defined in Section 6.1.2. For patients who have received localized therapy (embolization, chemoembolization, radiofrequency ablation or radiation) are eligible if measurable disease is not within the treatment field or the treated disease has clearly progressed since last localized therapy.

_____ 3.1.6 Patient must not have had major surgery within 14 days before randomization. Patients with surgery planned during study period are ineligible

_____ 3.1.7 Women must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.

All females of childbearing potential must have a blood test or urine study within 14 days prior to randomization to rule out pregnancy.

A female of childbearing potential is defined as any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female of child bearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.1.8 Women of childbearing potential and sexually active males must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in the study and continue for at least 4 months after the last dose of protocol treatment.

_____ 3.1.9 Male patients must not donate sperm during the course of this study or within 4 months after receiving their last dose of protocol treatment.

_____ 3.1.10 Female patients must not donate eggs (ova) during the course of this study or within 4 months after receiving their last dose of protocol treatment.

_____ 3.1.11 Patient must have adequate organ and marrow function, as defined below, obtained within 14 days prior to randomization.

_____ Leukocytes ≥ 3,000/mcL

Leukocytes: _____ Date of Test: _____

_____ Absolute neutrophil count ≥ 1,500/mcL

ANC: _____ Date of Test: _____

_____ Platelets ≥ 100,000/mcL

Platelet: _____ Date of Test: _____

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

Bilirubin: _____ Institutional ULN: _____

Date of Test: _____

Patient with Gilbert's syndrome: _____ (Yes or No)

_____ Hemoglobin ≥ 9g/dL

Hgb: _____ Date of Test: _____

_____ AST(SGOT)/ALT(SGPT) ≤ 2.5 × institutional ULN

ALT: _____ Institutional ULN: _____

Date of Test: _____

AST: _____Institutional ULN: _____

Date of Test: _____

_____ Creatinine ≤ institutional ULN, OR

Glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2

Note units and please refer to Appendix VII for the formula to estimate renal function using serum creatinine.

_____ Serum creatinine _____Date of Test: _____

GFR: _____Date of Test: _____

_____ 3.1.12 Patient must not have a prolonged rate corrected QT (QTc) interval ≥ 480 msec calculated according to institutional guidelines.

_____ 3.1.13 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial. Known HIV positive patients who meet the following criteria will be considered eligible:

- CD4 count ≥ 350cells/mm^3
- Undetectable viral load
- Maintained on modern therapeutic regimens utilizing non-CYP interactive agents (i.e. excluding ritonavir)
- No history of AIDS-defining opportunistic infections

_____ 3.1.14 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

_____ 3.1.15 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

_____ 3.1.16 Patients who have not recovered from adverse events due to prior anti-cancer therapy (i.e. have residual toxicities > grade 1) are ineligible with the exception of alopecia.

_____ 3.1.17 Patients with persistent ≥ grade 2 diarrhea lasting more than 3 consecutive days within 14 days of randomization are ineligible.

_____ 3.1.18 Patients who received prior platinum or taxane chemotherapy are eligible.

_____ 3.1.19 Patients with known central nervous system (CNS) involvement are ineligible.

_____ 3.1.20 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.

_____ 3.1.21 Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better. In addition, patients will any of the known cardiopulmonary disease, defined as follows, would be ineligible for this trial:

- Unstable angina
- Congestive heart failure (New York Heart Association [NYHA] Class III or IV;);
- Myocardial infarction within 6 months prior to randomization (patients who had ischemic heart disease such as acute coronary syndrome [ACS], myocardial infarction, and/or revascularization greater than 6 months before randomization and who are without cardiac symptoms may enroll)
- Symptomatic cardiomyopathy
- Clinically symptomatic pulmonary hypertension requiring pharmacologic therapy
- Clinically significant arrhythmia, defined as:
    1. History of polymorphic ventricular fibrillation or torsade de pointes,
    2. Permanent atrial fibrillation, defined as continuous atrial fibrillation for ≥ 6 months,
    3. Persistent atrial fibrillation, defined as sustained atrial fibrillation lasting > 7 days and/or requiring cardioversion in the 4 weeks before randomization,
    4. Grade 3 atrial fibrillation defined as symptomatic and incompletely controlled medically, or controlled with device (*e.g.*, pacemaker), or ablation
    5. Patients with paroxysmal atrial fibrillation or Grade < 3 atrial fibrillation for period of at least 6 months are permitted to enroll provided that their rate is controlled on a stable regimen.

_____ 3.1.22 Patient must not be receiving any other investigational agents.

_____ 3.1.23 Patient must not have received chemotherapy or radiotherapy within 2 weeks prior to randomization. Prior treatment with radiation therapy involving ≥ 25% of hematopoietically active bone marrow will be ineligible.

_____ 3.1.24 Patient must not have received immunotherapy within 8 weeks prior to randomization.

_____ 3.1.25 Patient must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to pevonedistat, carboplatin, or paclitaxel.

_____ 3.1.26 Patient must not be receiving any treatment with clinically significant metabolic enzyme inducers within 14 days before the first dose of the study drug as below. Clinically significant metabolic enzyme inducers are not permitted during the study. Patients must not be receiving any medications or substances that are strong inducers of CYP3A4/5 (i.e. phenytoin, rifampin, St. Johns wort) or inhibitors of BCRP (i.e. cyclosporine). Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if a new medication need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product. Inhibitors of CYP3A4/5 are allowed.

_____ 3.1.27 Patient must not have uncontrolled intercurrent illness.

_____ 3.1.28 Patient must not have uncontrolled coagulopathy or bleeding disorder.

_____ 3.1.29 Patient must not have active, uncontrolled infection or severe infectious disease such as severe pneumonia, meningitis, or septicemia.

_____ 3.1.30 Patient with known moderate chronic obstructive pulmonary disease, interstitial lung disease, and pulmonary fibrosis are ineligible.

_____ 3.1.31 Patient must not have psychiatric illness/social situations that would limit compliance with study requirements.

_____ 3.1.32 Patient must have the ability to understand and the willingness to sign a written informed consent document.

_____ 3.1.33 Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.

_____ 3.1.34 Patient must not have had prior pevonedistat treatment.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

4. Registration and Randomization Procedures

CTEP Registration Procedures

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

RCR utilizes five-person registration types.

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

RCR requires the following registration documents:

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

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

- Addition to a site roster;
- Assign the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN;
- Act as the site-protocol Principal Investigator (PI) on the IRB approval.

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

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

CTSU Registration Procedures

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

IRB Approval:

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

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

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

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

Additional Requirements

Additional requirements to obtain an approved site registration status include:

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

Downloading Site Registration Documents:

Site registration forms may be downloaded from the EA2187 protocol page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a PO on the protocol.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the (ECOG-ACRIN) link to expand, then select trial protocol #EA2187
- Click on LPO Documents, select the Site Registration documents link, and download and complete the forms provided. (Note: For sites under the CIRB initiative, IRB data will load automatically to the CTSU as described above.)

Submitting Regulatory Documents

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

To access the Regulatory Submission Portal log on to the CTSU members' website: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

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

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

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

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within fourteen working days after registration.

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

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Be on a LPO roster, ETCTN Corresponding roster, or PO roster with the role of Registrar. Registrars must hold a minimum of an AP registration type; and
- Have an approved site registration for a protocol prior to patient enrollment.

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

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

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

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

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

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

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

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

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

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

4.1 Patient Registration

The following information is to be provided at the time of registration to the trial:

4.1.1 Protocol Number

4.1.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.1.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.2 Additional Requirements

4.2.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.2.2 Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. To access Rave via iMedidata, site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account; and assigned one of the following Rave roles on the relevant Lead Protocol Organization (LPO) or Participating Organization roster at the enrolling site: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator. Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required. To the hold Rave CRA role or Rave CRA (Lab Admin) role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

4.2.3 Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the

"accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the Rave EDC link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a Rave EDC link will display under the study name.

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

4.2.4 Central monitoring

Central Monitoring (CM) Review is required for this protocol. CM allows Lead Protocol Organizations (LPOs) to remotely compare data entered in Rave to source documentation to ensure that sites are adhering to the protocol and central monitoring plan as well as accurately transcribing data from patients' charts (i.e., source data verification).

Sites can upload source documents required for CM Review as documented in the central monitoring plan using the Source Document Portal (SDP). This application is available on the CTSU members' website under Auditing & Monitoring and may also be accessed using a direct link within Rave on the CM Alert form. Site staff with the CRA or Investigator roles in Rave can view and upload source documents. Prior to saving source documents on the SDP, each site is responsible for removing or redacting any Personally Identifiable Information (PII) (note that functionality to do this redaction exists within the SDP itself). Designated LPO staff will review each document after it has been loaded on the SDP to ensure the appropriate documents have been uploaded and to ensure PII is redacted.

Additional information on the SDP is available on the CTSU members' website under Auditing & Monitoring > Source Document Portal in the Help Topics button or by contacting the CTSU Help Desk (1-888-823-5923 or ctsucontact@westat.com).

4.3 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA2187 Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

Treatment will be administered on an outpatient basis. All doses are based on actual body weight. Body surface area (BSA) should be recalculated if ≥ 5% weight change. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.1.1 Arm A: Pevonedistat Monotherapy

Pevonedistat: 50mg/m^2 intravenously (IV) over 60 minutes (±10 minutes) on days 1, 3, and 5

1 cycle = 21 days.

Repeat cycles until disease progression, unacceptable toxicity, or patient desire to discontinue study therapy.

Patients must not be receiving any medications or substances that are strong inducers of CYP3A4/5 (i.e., phenytoin, rifampin, St. John's wort) or inhibitors of BCRP (i.e., cyclosporine). Please see details in Appendix VI.

5.1.1.1 Pevonedistat Administration and Premedications

Pevonedistat is to be administered using a 250 mL D5W (5% dextrose in water) IV bag through central or peripheral venous access. The drug should be diluted in 5% dextrose to a final volume of 250 mL per instructions in Section 8.1.6. The IV infusion can be slowed or stopped and restarted for any associated infusion-related reactions. The total time from the IV preparation to the end of IV infusion must not exceed 6 hours. Infusion line can be flushed with 5% dextrose in water immediately after IV administration is complete.

5.1.2 Arm B: Pevonedistat in Combination with Carboplatin and Paclitaxel

Regimen Description					
Agent	Premedications; Precautions	Dose	Route	Schedule	Cycle Length
Paclitaxel	Dexamethasone 5-HT3 antagonist Diphenhydramine Ranitidine	175 mg/m^2	IV infusion over 3 hours	Day 1	21 days (3 weeks)
Carboplatin	Dexamethasone 5-HT3 antagonist	AUC=5	IV infusion over 15-60 minutes	Day 1	
Pevonedistat		20 mg/m^2	IV infusion over 1 hour	Days 1, 3, 5	
AUC= area under the curve					

Pevondedistat: 20 mg/m^2 IV over 60 minutes (±10 minutes) on days 1, 3, and 5 every cycle x 4, followed by:

Paclitaxel: 175mg/m^2 IV over 3 hours (+ 20 minutes), or utilizing local standard procedures, on day 1 of every cycle x 4, followed by:

Carboplatin: AUC 5 IV over 15-60 minutes on day 1 of every cycle x 4

1 cycle = 21 days.

Infusion times of paclitaxel and carboplatin may be adjusted/altered to meet local institutional standards.

Avoid the concomitant use of inhibitors or inducers of CYP2C8 and CYP3A4 during Arm B of the study as paclitaxel is metabolized by these enzymes. Avoid the concomitant use of nephrotoxic drugs during Arm B of the study as carboplatin may potentiate the renal effects of these drugs.

At any time after 4 cycles of combination therapy, the treating physician is given discretion whether to continue with:

Option a:

Pevonedistat

50 mg/m^2 on days 1, 3, & 5 every cycle OR

Option b:

Pevonedistat

20 mg/m^2 IV on days 1, 3, & 5 every cycle, followed by:

Paclitaxel

175 mg/m^2 on day 1 every cycle, followed by:

Carboplatin

AUC 5 IV on day 1 every cycle

Both option a and b treatment will continue until disease progression, unacceptable toxicity, or patient desire to discontinue study therapy. If a patient continues with option b, subsequent change to option a at later time points is permissible.

If the patient required a dose reduction attributable to pevonedistat then the patient should be maintained at the single agent dose of pevonedistat that they were already dose reduced to.

5.1.2.1 Pevonedistat Administration and Premedications

Pevonedistat is to be administered using a 250 mL D5W (5% dextrose in water) IV bag through central or peripheral venous access. Pevonedistat should be administered prior to carboplatin and paclitaxel. The drug should be diluted in 5% dextrose to a final volume of 250 mL per instructions in Section 8.1.6. The IV infusion can be slowed or stopped and restarted for any associated infusion-related reactions. The total time from the IV preparation to the end of IV

infusion must not exceed 6 hours. Infusion line can be flushed with 5% dextrose in water immediately after IV administration is complete.

5.1.2.2 Carboplatin Administration and Dose Calculation

Carboplatin at the appropriate dose will be given intravenously as a 30- minute infusion in Dextrose 5% in Water or Sodium Chloride 0.9%, volume per institutional standard.

Carboplatin dose will be calculated using the Calvert formula:

Total Dose (mg) = target AUC (GFR+25)

NOTE: Calculated total dose is in mg not mg/m^2

Substitute GFR with Creatinine Clearance (CrCl). CrCl will be calculated using the Cockcroft-Gault formula:

$$CrCl = \frac{(140 - age) * weight(kg)}{72 * serum\ creatinine} * (0.85\ if\ female)$$

The minimum serum creatinine value used will be 0.7 mg/dL, and the CrCl (or GFR) will be capped at 125 mL/min. Questions about this calculation should be directed to the Study Chair (also see Appendix VII). This calculation does not require to normalize to 1.73m^2, as is done for the eligibility criteria GFR.

NOTE: Remember to re-calculate the dose for each treatment cycle. The actual body weight should be used for all calculations

5.1.2.3 Paclitaxel Administration and Premedications

Paclitaxel should be diluted in Dextrose 5% or Sodium Chloride 09% per institutional standard and given by intravenous administration. The concentration of the final solution should be between 0.3 and 1.2 mg/mL. Prepare in non-PVC infusion container and administer IV over one hour via 0.22 micron in line filter and non-DEHP tubing. The calculated dose of paclitaxel should be administered via a free-flowing intravenous line as a 3 hour infusion. Solution exhibiting excessive particulate formation should be discarded.

Concentrations of up to 1.2 mg/mL in 5% dextrose or normal saline solution have demonstrated chemical and physical stability for at least 27 hours at room temperature.

On day 1 of each cycle, patients will receive dexamethasone pre-medication per institutional standards for paclitaxel. Due to known allergic reactions to paclitaxel and/or of the Cremophor® vehicle, the following precautions must be taken to minimize the chances of a hypersensitivity reaction.

Suggested pre-medications for Paclitaxel

Agent	Dose	Route	Duration
Dexamethasone	20 mg*	PO	12 and 6 hours prior to paclitaxel
5-HT3 Antagonist	**	PO	Per institutional guidelines, prior to infusion of paclitaxel
Diphenhydramine	50 mg	IV	30 minutes prior to paclitaxel
Ranitidine	50 mg	IV	30 minutes prior to paclitaxel

* 20 mg is the dose for cycle 1, day 1. Subsequently, may be decreased to 12 mg on cycle 2 day 1 and to 8 mg on cycle 3 day 1 and all future doses of paclitaxel. Alternatively, a single intravenous dose of 20 mg, 30 minutes prior to Paclitaxel (Taxol) injection, only when in the investigator's opinion, patients may have been non-adherent with oral pre-medication.

** Dose to be based on 5-HT3 Antagonist used.

Epinephrine and diphenhydramine for injection should be readily available during the infusion for emergency treatment of hypersensitivity reactions.

NOTE: Pre-medications can be adjusted/altered to meet local institutional standards.

5.2 Adverse Event Reporting Requirements

All toxicity grades described throughout this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.2.2 Routine Reporting of Adverse Events (Medidata Rave)

Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to Section 4 of the protocol for more information on how to access the Medidata Rave system and the EA2187 forms packet for instructions on what, where and when adverse events are to be reported routinely.

5.2.3 Expedited reporting of Adverse Events (CTEP-AERS)

In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

5.2.4 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours)
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - A congenital anomaly/birth defect

- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains a list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.2.5 Expedited Adverse Event Reporting Procedure

This protocol is a Medidata Rave-CTEP-AERS Integration study.

The general procedures outlined below describe how to report an Adverse Event (AE) requiring expedited reporting on an Integration study.

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

AEs that occur after baseline are reported in Medidata Rave according to the instructions on the EA2187 Adverse Events Form/Late Adverse Events Form, including those that start during the report period, persist from the previous report period, or increase in grade since baseline. AEs that occur prior to the start of treatment are reported on the EA2187 Baseline Adverse Events Form which is not be included in the Medidata Rave-CTEP-AERS Integration.

Prior to sending AEs through the rules evaluation process to determine if expedited reporting is required, the site must verify the following on the EA2187 Adverse Events Form/Late Adverse Events Form in Medidata Rave:

- The reporting period (course/cycle) is correct and
- AEs are recorded and complete (no missing fields) and the form is query free

Upon completion of AE entry in Medidata Rave, the site must then submit the AE for rules evaluation by completing the Expedited Reporting Evaluation Form. Both NCI and EA2187 protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for all AEs that meet expedited reporting requirements. The site must then complete the expedited report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

NOTE: The site must report AEs in Rave at the time the investigator learns of the event.

NOTE: If an AE reported on the EA2187 Adverse Events Form is modified, it must be re-submitted for rules evaluation.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900)
- the NCI (301-897-7497)

Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the Medidata Rave-CTEP-AERS Integration system is available on the CTSU website:

CTEP's guidelines for expedited AE reporting and CTEP-AERS can be found at http://ctep.cancer.gov.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 897-7404) in the same timeframe.

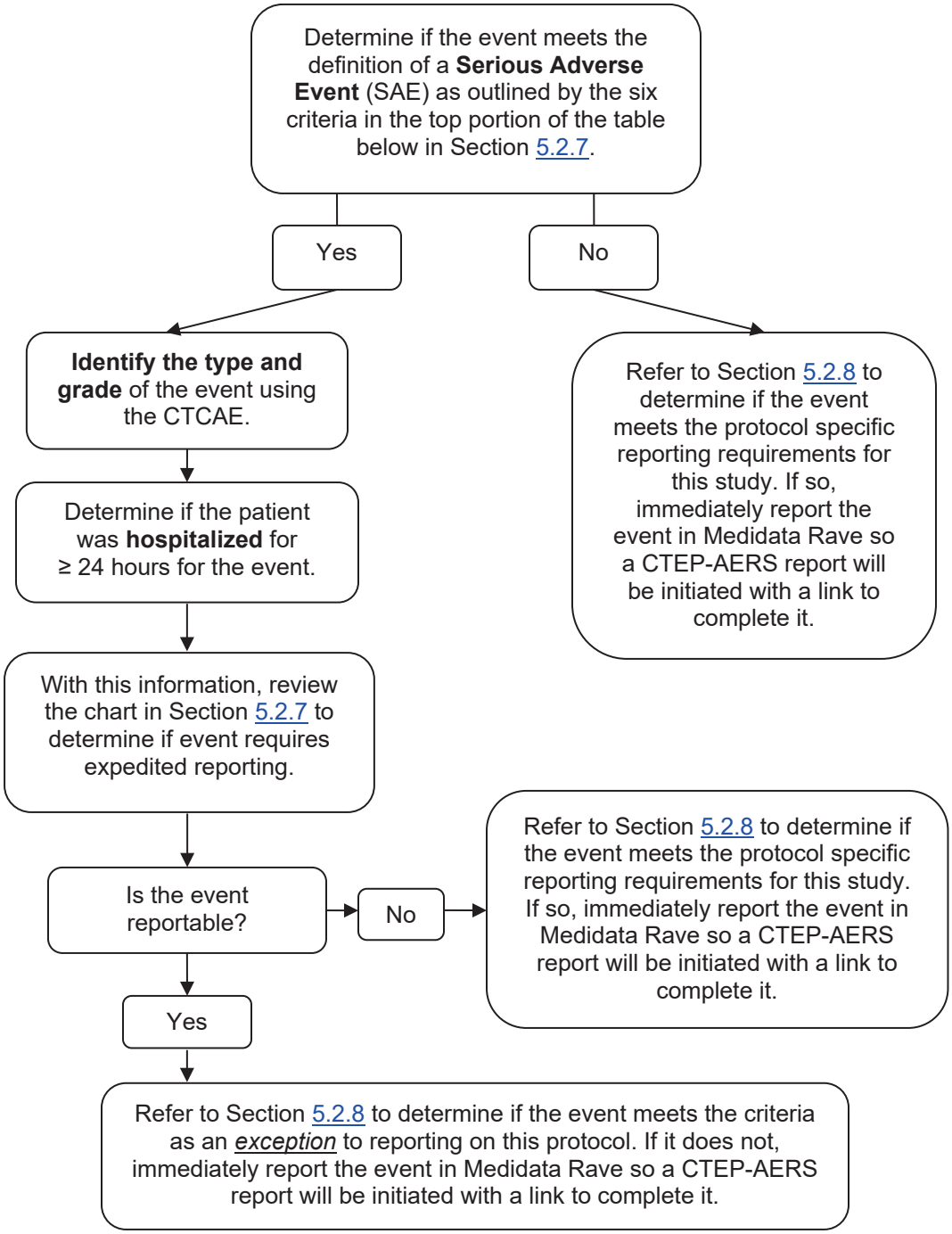
CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

Many factors determine the requirements for expedited reporting of adverse events on each individual protocol. The instructions and tables in the following sections have been customized for protocol EA2187 and outline the specific expedited adverse event reporting requirements for study EA2187.

5.2.6 Guidelines for determining if an adverse event is to be reported in an expedited manner – Arms A and B

- Site must determine if an event meets expedited reporting requirements so that the AE will be entered into Medidata Rave, triggering a CTEP-AERS report, within the mandated timeframes outlined in Section 5.2.7.
- Do not initiate the CTEP-AERS report via the CTEP-AERS website.
- We encourage all sites to confirm the Rules Engine assessment with the charts and tables below.
- Once the CTEP-AERS is completed, ECOG-ACRIN, the NCI, and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

5.2.6.1 Guidelines for reporting adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.2.6.2 Guidelines for reporting adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.7 OR the protocol specific requirements in Section 5.2.8 AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4 and Grade 5 AEs

  NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported expeditiously through CTEP-AERS even if the patient is off study.

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization

5.2.7 Expedited Reporting Requirements for Arms A and B on protocol EA2187

Investigational Agents: Pevonedistat

Commercial Agents: Carboplatin, Paclitaxel (Arm B only)

When an investigational agent is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.

Phase 1 and Early Phase 2 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI in CTEP-AERS accessed via Medidata Rave within the timeframes detailed in the table below.

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

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1] Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

5.2.8 Additional instructions, requirements and exceptions for protocol EA2187

Additional Instructions

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events in CTEP-AERS accessed via Medidata Rave, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study:** A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "*Disease progression*" under the System Organ Class (SOC) "*General disorder and administration site conditions*". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

EA2187 specific expedited reporting requirements:

- **Infusion Reaction:** Any grade 3 or greater hypersensitivity/infusion reaction (see Section 5.4.2.6) must be reported in Medidata Rave, triggering a CTEP-AERS report, within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- **Pregnancies**: Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on Pevonedistat, or within 28 days of the female patient's last dose of Pevonedistat, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported in Medidata Rave first, which will trigger a CTEP-AERS report, within 24 hours of the Investigator's knowledge. Please refer to Appendix V for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EA2187 specific expedited reporting exceptions:

For study Arms A and B, the adverse events listed below **do not** require expedited reporting:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported

expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.2.9 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.10 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave.

- **A second malignancy is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A secondary malignancy is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.

     Report the diagnosis expeditiously by initially reporting it on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the secondary malignancy is entered into Rave, the CTEP-AERS report must then be initiated directly from the link generated from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.

If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted in CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pevonedistat HCl (MLN4924, NSC793435)

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

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

Version 2.3, July 10, 2020[1]

Adverse Events with Possible Relationship to MLN4924 (Pevonedistat HCl) (CTCAE 5.0 Term) [n= 474]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
CARDIAC DISORDERS			
		Sinus tachycardia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
	Pain		***Pain (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Lung infection		***Lung infection (Gr 2)***
	Upper respiratory infection		
	Urinary tract infection		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		***Bruising (Gr 2)***

Adverse Events with Possible Relationship to MLN4924 (Pevonedistat HCl) (CTCAE 5.0 Term) [n= 474]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
INVESTIGATIONS			
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
	GGT increased		
	Platelet count decreased		***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
	Hypercalcemia		
	Hyperglycemia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***
	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		***Muscle cramp (Gr 2)***
Myalgia			***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
	Nervous system disorders - Other (neuropathy peripheral, peripheral neuropathy)		
	Paresthesia		
PSYCHIATRIC DISORDERS			
	Anxiety		
	Confusion		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***

Adverse Events with Possible Relationship to MLN4924 (Pevonedistat HCl) (CTCAE 5.0 Term) [n= 474]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Epistaxis		
	Hypoxia		
	Pleural effusion		
	Productive cough		
	Respiratory, thoracic and mediastinal disorders - Other (rales)		
	Wheezing		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		
	Purpura		
VASCULAR DISORDERS			
	Hypotension		***Hypotension (Gr 2)***

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocarditis

EYE DISORDERS - Blurred vision

GASTROINTESTINAL DISORDERS - Ascites; Dyspepsia; Gastrointestinal disorders - Other (gastrointestinal necrosis); Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Ileus; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Generalized edema; Multi-organ failure; Non-cardiac chest pain

HEPATOBILIARY DISORDERS - Hepatic failure

INFECTIONS AND INFESTATIONS - Bacteremia; Sepsis; Sinusitis; Skin infection

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall

INVESTIGATIONS - Investigations - Other (brain natriuretic peptide increased); Neutrophil count decreased; Weight loss; White blood cell decreased

METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hyperuricemia

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy

NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Spinal cord compression

PSYCHIATRIC DISORDERS - Psychiatric disorders - Other (mental status changes)

RENAL AND URINARY DISORDERS - Dysuria; Renal and urinary disorders - Other (renal impairment); Urinary retention

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Nasal congestion; Oropharyngeal pain; Respiratory failure; Rhinorrhea

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular

VASCULAR DISORDERS - Hypertension; Phlebitis; Thromboembolic event

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

5.4 Dose Modifications

Patients must meet the following treatment parameters for each cycle:

Parameter	Day 1	Days 3 and 5
Absolute Neutrophil Count (ANC)	≥ 1 ,000/mcL	≥ 1 ,000/mcL
Hemoglobin	≥ 8.0 g/dL	≥ 8.0 g/dL
Platelet Count	≥ 100,000/mcL	≥ 75,000/mcL
Total Bilirubin	≤ 1.5 x ULN or baseline if >ULN	≤ 1.5 x ULN or baseline if >ULN
AST (SGOT)/ALT (SGPT)	≤ 3.0 x ULN; ≤ 5 x ULN in setting of metastatic liver disease	≤ 3.0x ULN; ≤ 5 x ULN in setting of metastatic liver disease
Creatinine/CrCL	≤ institutional ULN	Not applicable

Laboratory assessments must be done and results reviewed by a treating physician prior to each pevonedistat administration.

All other toxicities (except alopecia, lymphopenia, hyperglycemia, hypoalbuminemia, fatigue, elevated serum alkaline phosphatase, neuropathy [see Section 5.4.2.1], and hemoglobin [see Section 5.4.1.3]) at least possibly related to study treatment should have resolved to grade 1 or lesser severity or pre-study baseline before initiation of the next cycle of therapy. Furthermore, dose modifications for white blood cell (WBC) or other components of the differential (such as lymphocytes, monocytes) are not planned and therefore, not included.

Dose holds and modifications are made according to the organ system showing the greatest degree of toxicity. Toxicity will be graded using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

Tables below are general guidance for adverse events. Treating physicians may use discretion to hold or reduce dose for these events with the approval of the Study Chair.

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 investigator. If a patient fails to meet the criteria for retreatment, initiation of the next cycle of treatment may be delayed for up to 3 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 >3 weeks because of incomplete recovery from treatment related toxicity. If the reduced dose is well tolerated and the toxicity leading to dose reduction was ≤Grade 3, has resolved, and does not reoccur, the dose may resume at the original dose level in the next cycle after endorsement by the investigator (or designee).

For toxicity not related to drug (eg, disease-related toxicity), although a similar dose reduction is permitted, in general it is discouraged. If the dose is well tolerated and the toxicity leading to dose reduction was ≤ Grade 3, has resolved,

and does not reoccur, the dose may resume at the original dose level in the next cycle.

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 investigator (or designee) agrees that it is in the patient's interest to continue therapy with the study drug(s), then after recovery of the toxicity or toxicities in question to ≤Grade 1 or to the patient's baseline values, the dose of study drug may be reduced in the next cycle. For toxicity not related to drug (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 investigator (or designee). Initiation of the next cycle of therapy may be delayed no more than 3 weeks to allow recovery from toxicity. Treatment delay of > 3 weeks to all protocol therapy due to a toxicity at least possibly related to study drugs will lead to removal of the patient from the study treatment. If all treatment related toxicities do not recover within 3 weeks to the point where patients meet re-treatment criteria above, then patients should be removed from study treatment.

Dose reductions are permitted until pevonedistat dose is 10mg/m^2 for the combination therapy and 25mg/m^2 for the monotherapy. If untoward toxicity persists despite dose adjustments or if more than 2 dose reductions for the combination therapy or 3 dose reductions for the monotherapy are required, the patient will be removed from protocol treatment.

Since fatigue is multifactorial and can be a symptom of cancer progression, dose reduction for fatigue will only be done if the fatigue is deemed to be drug-related in the opinion of the investigator.

Dose Modification Levels

Arm A:

Dose Level	Pevonedistat (monotherapy therapy)
0	50 mg/m^2
-1	44 mg/m^2
-2	33 mg/m^2
-3	25 mg/m^2

Arm B:

Dose Level	Carboplatin	Paclitaxel	Pevonedistat (combination therapy)
0	AUC 5	175 mg/m^2	20 mg/m^2
-1	AUC 4	125 mg/m^2	15 mg/m^2

Dose Level	Carboplatin	Paclitaxel	Pevonedistat (combination therapy)
-2	AUC 3	100 mg/m^2	10 mg/m^2
-3	N/A	N/A	N/A

5.4.1 Hematologic Toxicity

5.4.1.1 Neutrophils

The following dose adjustments are based on the lowest neutrophil count of the preceding treatment course.

Neutropenia	**Management/Next Dose for Pevonedistat**	**Management/Next Dose for Paclitaxel**	**Management/Next Dose for Carboplatin**
≤ Grade 1/2	No change in dose	No change in dose	No change in dose
Grade 3/4 (≤ 7 days and without fever)	Hold* until ≤ Grade 2. Resume at same dose level.	Hold* until ≤ Grade 2. Resume at same dose level.	Hold* until ≤ Grade 2. Resume at same dose level.
Grade 3/4 (>7 days or any duration with fever 1st episode	Hold* until ≤ Grade 2. Resume at same dose level.	Hold* until ≤ Grade 2. Resume at same dose level.	Hold* until ≤ Grade 2. Resume at same dose level.
Grade 3/4 (>7 days or any duration with fever 2nd episode	Hold* until ≤ Grade 2. Reduce by 1 dose level.**	Hold* until ≤ Grade 2. Reduce by 1 dose level.**	Hold* until ≤ Grade 2. Reduce by 1 dose level.**

*Patients requiring a delay of all protocol therapy > 3 weeks due to toxicity should go off protocol therapy.

**Patients requiring > two dose reduction of chemotherapy should go off protocol therapy. If a toxicity leads to a hold on day 1 of a cycle, the whole cycle is to be delayed until the toxicity meets treatment criteria. If a toxicity leads to a hold of pevonedistat during the cycles (i.e. day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

NOTE: Use of prophylactic granulocyte colony stimulating factor is permitted per investigator discretion. Use of ASCO guidelines is recommended.

5.4.1.2 Platelets

Thrombocytopenia	Management/Next Dose for Pevonedistat	Management/Next Dose for Paclitaxel	Management/Next Dose for Carboplatin
≤ Grade 1	No change in dose	No change in dose	No change in dose
Grade 2	For Day 1 of any cycle, hold* until ≥ 100,000. Resume at same dose level.	For Day 1 of any cycle, hold* until ≥ 100,000. Resume at same dose level.	For Day 1 of any cycle, hold* until ≥ 100,000. Resume at same dose level.
Grade 3/4 ≤ 7 days and no clinically significant bleeding and > 10,000 mcL	For Day 1 of any cycle, hold* until ≥ 100,000. Resume at same dose level.	For Day 1 of any cycle, hold* until ≥ 100,000. Resume at same dose level.	For Day 1 of any cycle, hold* until ≥ 100,000. Resume at same dose level.
Grade 3/4 lasting > 7 days or requiring prophylactic platelet transfusion (≤ 10,000 mcL) 1st episode	For Day 1 of any cycle, hold* until ≥ 100,000. Reduce by 1 dose level.	For Day 1 of any cycle, hold* until ≥ 100,000. Resume at same dose level.	For Day 1 of any cycle, hold* until ≥ 100,000. Reduce by 1 dose level.
Grade 3/4 lasting > 7 days or requiring prophylactic platelet transfusion (≤ 10,000 mcL) 2nd episode	For Day 1 of any cycle, hold* until ≥100,000. Reduce by 1 dose level.**	For Day 1 of any cycle, hold* until ≥100,000. Reduce by 1 dose level.**	For Day 1 of any cycle, hold* until ≥ 100,000. Reduce by 1 dose level. **
Grade 3/4 of any duration with clinically significant bleeding * **	Off study treatment	Off study treatment	Off study treatment

*Patients requiring a delay of all protocol therapy >3 weeks due to toxicity should go off protocol therapy.

**Patients requiring > two dose reduction of chemotherapy should go off protocol therapy. If a toxicity leads to a hold on day 1 of a cycle, the whole cycle is to be delayed until the toxicity meets treatment criteria. If a toxicity leads to a hold of pevonedistat during the cycles (i.e. day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

***Clinically significant bleeding for this protocol is defined as potentially serious or life-threatening (i.e. GI bleed, intracranial hemorrhage). Patients with more minor bleeding may be continued on study treatment.

5.4.1.3 Hemoglobin

The hemoglobin parameters must meet the criteria specified in the table at the beginning of Section 5.4 on day 1 of each treatment cycle. Treatment should be delayed until recovery of the counts to the specified levels. Supportive transfusion is permitted after cycle 1, day 1 and future cycles for subjects who do not meet hemoglobin parameters for retreatment.

5.4.2 Non-Hematologic Toxicity

5.4.2.1 Peripheral Sensory Neuropathy

The following dose adjustments are based on the worst grade experience of sensory neuropathy of any preceding treatment course.

Sensory Neuropathy	Management/Next Dose for Pevonedistat	Management/Next Dose for Paclitaxel	Management/Next Dose for Carboplatin
≤ Grade 1	No change in dose	No change in dose	No change in dose
Grade 2, tolerable and <7 consecutive days	No change in dose	No change in dose	No change in dose
Grade 2, intolerable or >7 consecutive days	No change in dose	Hold* until < Grade 2. Reduce by 1 dose level.**	No change in dose
Grade 3	No change in dose	Discontinue paclitaxel[#]	Hold* until < Grade 2. Reduce by one dose level.**
Grade 4	Off study	Off study	Off study

* Patients requiring a delay of all protocol therapy >3 weeks due to toxicity should go off protocol therapy.

**Patients requiring > two dose reduction of chemotherapy should go off protocol therapy. If a toxicity leads to a hold on day 1 of a cycle, the whole cycle is to be delayed until the toxicity meets treatment criteria. If a toxicity leads to a hold of pevonedistat during the cycles (i.e. day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

[#] After 4 cycles, paclitaxel may be discontinued for neuropathy and patient may continue with other study agents.

5.4.2.2 Arthralgia/Myalgia

Arthralgia/Myalgia	Management/Next Dose for Pevonedistat	Management/Next Dose for Paclitaxel	Management/Next Dose for Carboplatin
≤ Grade 1	No change in dose	No change in dose	No change in dose
Grade 2[#]	No change in dose	Hold* until < Grade 2. Reduce by 1 dose level.**	No change in dose
Grade 3	Hold* until < Grade 2. Reduce by 1 dose level.**	Hold* until < Grade 2. Reduce by 1 dose level.**	No change in dose

* Patients requiring a delay of all protocol therapy >3 weeks due to toxicity should go off protocol therapy.

**Patients requiring > two dose reduction of chemotherapy should go off protocol therapy. If a toxicity leads to a hold on day 1 of a cycle, the whole cycle is to be delayed until the toxicity meets treatment criteria. If a toxicity leads to a hold of pevonedistat during the cycles (i.e. day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

[#]For the first occurrence of grade 2 myalgia/arthralgia, dexamethasone can be administered for 3-4 days (approximately 4mg BID) after chemotherapy. If symptoms recur despite this, the next dose of paclitaxel will be reduced by 1 dose level.

5.4.2.3 Hepatic Toxicity

There are no dose adjustments for carboplatin based on hepatic toxicity. Dose adjustments are for hepatoxicity at least possibly related to pevonedistat or paclitaxel.

AST and/or ALT **Use ULN**	**Management/Next Dose for Pevonedistat**	**Management/Next Dose for Paclitaxel**	**Management/Next Dose for Carboplatin**
Grade 1: >1-3 x ULN	No change in dose	No change in dose	No change in dose
Grade 2: >3-5 x ULN	Hold* until meets treatment parameter, no change in dose level	Hold* until meets treatment parameter, no change in dose level	Hold until meets treatment parameter, no change in dose level
Grade 3: >5-20 x ULN	Hold* until meeting treatment criteria and then reduce by 1 dose level	Hold* until meeting treatment criteria and then reduce by 1 dose level.	Hold until meets treatment parameter, no change in dose level
Grade 4:>20 x ULN	Off study treatment	Off study treatment	Off study treatment

Bilirubin **Use ULN**	**Management/Next Dose for Pevonedistat**	**Management/Next Dose for Paclitaxel**	**Management/Next Dose for Carboplatin**
Grade 1: >1-1.5 x ULN	No change in dose	No change in dose	No change in dose
Grade 2: >1.5-3 x ULN	Hold until meets treatment parameter, no change in dose level	Hold until meets treatment parameter, no change in dose level	Hold until meets treatment parameter, no change in dose level
Grade 3: >3-10 x ULN	Hold* until meeting treatment criteria and then reduce by 1 dose level.	Hold* until meeting treatment criteria and then reduce by 1 dose level.	Hold until meets treatment parameter, no change in dose level
Grade 4: >10 x ULN	Off study treatment	Off study treatment	Off study treatment

* Patients requiring a delay of all protocol therapy >3 weeks due to toxicity should go off protocol therapy.

**Patients requiring > two dose reduction of chemotherapy should go off protocol therapy. If a toxicity leads to a hold on day 1 of a cycle, the whole cycle is to be delayed until the toxicity meets treatment criteria. If a toxicity leads to a hold of pevonedistat during the cycles (i.e. day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

5.4.2.4 Gastrointestinal Toxicity

Nausea and/or vomiting should be controlled with adequate antiemetic therapy. Prophylactic anti-emetic therapy can be used at the discretion of the treating physician. Diarrhea should be managed with adequate anti-diarrheal medications. Patients are encouraged to take plenty of oral fluids. Dose holds and modifications are for symptoms at least possibly related to the study therapy and occurring despite maximal medical management.

Nausea**	**Management/Next Dose for Pevonedistat**	**Management/Next Dose for Paclitaxel**	**Management/Next Dose for Carboplatin**
≤ Grade 1	No change in dose	No change in dose	No change in dose
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.

After optimal anti-emetic therapy. Use of prophylactic or scheduled antiemetics are recommended in future cycles for patients experiencing grade 2 or higher nausea.

* Patients requiring a delay of all protocol therapy >3 weeks due to toxicity should go off protocol therapy.

**Patients requiring > two dose reduction of chemotherapy should go off protocol therapy. If a toxicity leads to a hold on day 1 of a cycle, the whole cycle is to be delayed until the toxicity meets treatment criteria. If a toxicity leads to a hold of pevonedistat during the cycles (i.e. day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

Vomiting**	**Management/Next Dose for Pevonedistat**	**Management/Next Dose for Paclitaxel**	**Management/Next Dose for Carboplatin**
≤ Grade 1	No change in dose	No change in dose	No change in dose
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
Grade 4	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.

After optimal anti-emetic therapy. Use of prophylactic or scheduled antiemetics are recommended in future cycles for patients experiencing grade 2 or higher nausea.

* Patients requiring a delay of all protocol therapy >3 weeks due to toxicity should go off protocol therapy.

**Patients requiring > two dose reduction of chemotherapy should go off protocol therapy. If a toxicity leads to a hold on day 1 of a cycle, the whole cycle is to be delayed until the toxicity meets treatment criteria. If a toxicity leads to a hold of pevonedistat during the cycles (i.e. day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

Diarrhea**	Management/Next Dose for Pevonedistat	Management/Next Dose for Paclitaxel	Management/Next Dose for Carboplatin
≤ Grade 1	No change in dose	No change in dose	No change in dose
Grade 2	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.	Hold* until ≤ Grade 1. Reduce by 1 dose level.
Grade 4	Off study treatment	Off study treatment	Off study treatment

After optimal anti-diarrheal therapy.

Recommended management: Loperamide anti-diarrheal therapy.

Dosage Schedule: 4 mg at first onset, followed by 2 mg with each loose bowel movement until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours).

Adjunct anti-diarrheal therapy is permitted and should be recorded when used.

* Patients requiring a delay of all protocol therapy >3 weeks due to toxicity should go off protocol therapy.

**Patients requiring > two dose reduction of chemotherapy should go off protocol therapy. If a toxicity leads to a hold on day 1 of a cycle, the whole cycle is to be delayed until the toxicity meets treatment criteria. If a toxicity leads to a hold of pevonedistat during the cycles (i.e. day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

5.4.2.5 Hypersensitivity Reaction

Caution: Patients who have a mild to moderate hypersensitivity reaction to paclitaxel and carboplatin may be re-challenged, but careful attention to prophylaxis and bedside monitoring of vital signs is recommended.

Hypersensitivity reactions to paclitaxel and/or carboplatin will be managed as follows:

Mild symptoms (*e.g.*, mild flushing, rash, pruritus) - Complete infusion. Supervise at bedside. No treatment required.

Moderate symptoms (*e.g.*, moderate rash, flushing, mild dyspnea, chest discomfort) -Stop infusion. Give intravenous diphenhydramine 25 mg and intravenous dexamethasone 10 mg. Resume infusion after recovery of symptoms at a low rate, 20 mg/hr. For 15 minutes, then, if no further symptoms, at full dose rate until infusion is complete. If symptoms recur, stop infusion. The patient should receive no additional paclitaxel and/or carboplatin for that cycle, but may be retreated after discussion with the principal investigator.

Severe life-threatening symptoms (*e.g.*, hypotension requiring pressor therapy, angioedema, respiratory distress requiring bronchodilation therapy, generalized urticaria)- stop infusion. Give intravenous diphenhydramine and

dexamethasone as above. Add epinephrine or bronchodilators if indicated. If wheezing is present, that is not responsive to bronchodilators, epinephrine is recommended. Patient should be removed from further protocol therapy. Report as serious adverse event (see Section 5.2).

5.4.2.6 Other toxicities

Fatigue: Grade 3 fatigue should be medically managed. If lasting more than 7 days, then all study treatment should be held until the fatigue recovers until grade 1 or less. The treatment may then be resumed at one dose level reduction of pevonedistat and/or paclitaxel and carboplatin. If attribution for fatigue is at least possibly related to pevonedistat, this agent alone should be reduced by one dose level. If attribution for fatigue is unlikely or unrelated to pevonedistat, then the chemotherapy agent(s) with attribution of at least possible related should be reduced by one dose level.

Electrolytes: Grade 3 or 4 depletion of electrolytes (*e.g.* K, Mg, Phos) should be optimally medically managed. If these persist for > 48 hours despite attempts at repletion, then all study treatment should be held until the electrolytes return to grade 1 or less. The treatment may then be resumed at one dose level reduction of pevonedistat, paclitaxel and/or carboplatin, if attribution at least possibly related to drug.

Other Adverse Events: For any grade 3 or 4 toxicity, not mentioned above, the treatment with the likely inciting agent should be withheld until the patient recovers to grade 1 or less toxicity. The treatment may then be resumed at one dose level reduction. For intolerable grade 2 toxicities, withhold treatment until the patient recovers, then resume treatment at a one dose level reduction. Dose reduction will be done for the drug that is most likely to have caused the toxicity. For grade 1 or tolerable grade 2 toxicities or clinically insignificant laboratory changes, no dose reduction should be made.

5.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

5.5.1 Growth Factor & Transfusions

The use of prophylactic growth factors should follow the American Society of Clinical Oncology (ASCO) guidelines and is not allowed for cycle 1; and could be administered per ASCO guidelines starting with cycle 2. Patients may receive red blood cell and platelet transfusions as clinically indicated by the treating physician. Empiric platelet transfusions are recommended for platelet count ≤ 10,000/mcL.

5.5.2 Supportive care agents for bone metastases

Patients with known metastatic disease to the bones are allowed to take bisphosphonates or denosumab as directed by the treating physician.

5.5.3 Post-treatment anti-emetic medications

It is recommended that patients be given take home prescriptions for an oral 5- HT3 antagonist (i.e. ondansetron, granisetron) to take as needed for nausea or emesis. Aprepitant or fosaprepitant are allowed on study per institutional standards.

5.5.4 Venous Thromboembolism

For patient who develop an indication to start anticoagulation during study therapy (i.e. a DVT or PE), anticoagulants including warfarin (with PT/INR monitoring), low molecular weight heparin, and factor Xa inhibitors are permitted and the patient may stay on trial as long as they personally have not developed grade 3 or worse thrombocytopenia or medically significant bleeding at the current dose level that they are receiving on trial.

5.5.5 Other

Because there is a potential for interaction of pevonedistat with other concomitantly administered drugs, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. Clinically significant metabolic enzyme inducers are prohibited/excluded during the study. The Study Chair should be alerted if the patient is taking any agent known to affect or with the potential for drug interactions. The study team should check a frequently-updated medical reference for a complete list of drugs to avoid or minimize use of. Appendix VI (Patient Drug Information Handout and Wallet Card) should be provided to patients if available.

Table Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	Agents such as acetaminophen and acetaminophen-containing compounds may be used judiciously and should not exceed a dose of 2 g of acetaminophen in a 24 hour period.
Systemic antineoplastic therapy, except for hydroxyurea	
Clinically significant metabolic enzyme inducers	Excluded IN THE STUDY In Arm B ONLY: Avoid the concomitant use of inhibitors or inducers of CYP2C8 and CYP3A4

Table Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
Known BCRP inhibitors (ie, cyclosporine)	Excluded **but limited use is permitted only if clinically necessary and no suitable alternative exists.** The patient may receive the BCRP inhibitor from 24 hours after the last pevonedistat dose until 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the BCRP inhibitor may be administered from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle. Avoid the concomitant use of nephrotoxic drugs IN Arm B of the study
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,

5.6 Duration of Therapy

Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA2187 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Patient experiences disease progression.
- Non-protocol therapies are administered.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 3 years from the date of randomization. Patients will undergo follow-up visits every 3 months for the first year, and every 6 months for years 2-3. All patients must also be followed through completion of all protocol therapy.

6. Measurement of Effect

6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [Eur J Ca 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in RECIST.

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before randomization.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Primary Evaluation of Response Rate

All patients who initiate study therapy will be used in the primary evaluation of the response rate.

6.1.2 Disease Parameters

Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥ 10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At

baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

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

Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before randomization.

The same method of assessment and the same technique must be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions

Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray

Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up must be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT

At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document

that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound

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

Endoscopy, Laparoscopy

The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology

These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

NOTE: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the

sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.4.2.

Stable Disease (SD)

Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 4 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

Disappearance of all non-target lesions. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-CR/Non-PD

Persistence of one or more non-target lesions.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

new effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient’s best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Overall Response	Best Overall Response when Confirmation is Required
CR	CR	No	CR	≥ 4 wks. Confirmation
CR	Non-CR***/Non-PD	No	PR	≥ 4 wks. Confirmation
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 4 wks. from study entry
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD***	Yes or No	PD***	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

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

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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

6.1.4.5 Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

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

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 4 weeks.

7. Study Parameters

7.1 Therapeutic Parameters

Advanced Disease Protocols

1. Prestudy scans, ECG, and x-rays used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to randomization.
2. Prestudy medical history, physical examination, vitals, performance status and CBC (with differential and platelet count) should be done ≤ 2 weeks before randomization.
3. All required prestudy chemistries, as outlined in Section 3, should be done ≤ 2 weeks before randomization – unless specifically required on Day 1 as per protocol.
4. The standard of care molecular testing submission and tissue submission should be completed within 4 weeks of randomization.

		Cycle 1					Cycle 2					Cycle 3			Cycle 4+					
	Prior to Rando-mization	Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	At disease progression	4 weeks after last dose of study drug[A]	Long term follow-up off study treatment
Demographics	X																			
Medical history[B]	X																			
Interval history[C]	X	X	X	X			X					X			X			X	X	
Concurrent meds	X	X	X	X			X					X			X			X		
Physical exam[C]	X	X	X	X			X					X			X			X	X	
Vital signs[C]	X	X	X	X			X	X	X			X	X	X	X	X	X	X	X	
Height	X																			
Weight[C]	X	X	X	X			X					X			X			X	X	
Performance status[C]	X	X	X	X			X					X			X			X	X	
CBC with differential	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

		Cycle 1					Cycle 2					Cycle 3			Cycle 4+					
	Prior to Rando-mization	Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	At disease progression	4 weeks after last dose of study drug[A]	Long term follow-up off study treatment
Chemistry panel[D]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy test[E]	X																			
Adverse event evaluation		X																		
Tumor measurements	X											X						X		X
CT or MRI Chest and Abdomen[F]	X											X						X		
CT or MRI Pelvis[G]	X											X						X		
SOC Molecular Testing Submission[H]	X																			
Tissue Submission[H]	X																			
ECG	X																			
Phone Follow-up																				X

A: A safety follow-up visit will occur 30 days (±7 days) after the last dose of treatment.

B Medical history to include prior treatments, radiation and surgical history, and smoking history. Diagnosis and staging to include pathology report and Tumor Node Metastasis (TNM) staging 8th edition.

C: At subsequent visits, symptom-directed history and physical examinations including vital signs, weight and performance status should be performed. Vital sign measurements will be taken with the patient in the supine or sitting position.

D: To include albumin, alkaline phosphatase, ALT, AST, bicarbonate, BUN, calcium, chloride, creatinine, GGT, glucose, lactate dehydrogenase, phosphorus, potassium, sodium, total bilirubin, and total protein. Before each dose of pevonedistat infusion laboratory must be done and results reviewed by a treating physician.

E: All females of childbearing potential must have a negative [blood test or urine test] within 14 days prior to randomization to rule out pregnancy.

F: CT or MRI scans of chest and abdomen will be done at baseline to assess the response per RECIST v1.1 criteria. CTs or MRIs with IV contrast

		Cycle 1					Cycle 2					Cycle 3			Cycle 4+					
	Prior to Rando-mization	Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	At disease progression	4 weeks after last dose of study drug[A]	Long term follow-up off study treatment
are encouraged but will be done at the investigator's discretion. CT imaging of chest and abdomen should occur after every 6 weeks (±7 days).																				
G CT or MRI scans of pelvis will be done at baseline to assess the response per RECIST v1.1 criteria. CTs or MRIs with IV contrast are encouraged but will be done at the investigator's discretion. CT imaging of pelvis should occur after every 6 weeks (±7 days), unless CT scans are negative at baseline, then they should be repeated as clinically indicated.																				
H SOC molecular testing and tissue submission should be completed within 4 weeks of randomization.																				
ALT=alanine aminotransferase, AST=aspartate aminotransferase, BUN=blood urea nitrogen, CBC=complete blood count, CT=computed tomography, CTC = circulating tumor cells, EKG=electrocardiogram, GGT=γ-glutamyl transferase, IV=intravenous, MRI=magnetic resonance imaging, NAE1 = neural precursor cell expressed developmentally downregulated protein 8 (NEDD-8) activating enzyme, PBMC=peripheral blood mononuclear cell, PK = pharmacokinetics, PO=orally, TSH=thyroid stimulating hormone.																				

Scheduled assessments every week are allowed a window of ± [3] days for day 1, 8 and 15 and +[1] day for days 3 and 5. Days 3 and 5 should not be done early. This window should be calculated from the scheduled date of the procedure/assessment. If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule.

7.2 Biological Sample Submissions

Samples are to be submitted as outlined in Section 10. Biological materials will be used in the correlative study described in Section 11.

All samples must be logged and tracked in the ECOG-ACRIN Sample Tracking System (STS).

Material	Prior to Start of Treatment	Ship To:
MANDATORY for Defined Laboratory Research Study		
Pre-Trial Diagnostic FFPE tumor tissue[1,2]	X	E-A CBPF

1. Submit within 4 weeks of registration to trial.
2. Submission is required, if specimen is available. New biopsy is not required.

8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Agent Ordering and Agent Accountability:

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

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an “active” account status, a “current” password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB’s website for specific policies and guidelines related to agent management.

Agent Inventory Records:

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

Investigator Brochure Availability:

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

NCI Supplied Agent(s) – General Information

NOTE: Under no circumstances can commercially supplied pevonedistat be used or substituted for the NCI-supplied pevonedistat.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time or email PMBAfterHours@mail.nih.gov anytime.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. A separate NCI Investigational Agent Accountability Record must be maintained for each patient sequence number and for each agent on this protocol.

Useful Links and Contacts:

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

8.1 Pevonedistat HCl (MLN4924, NSC 793435)

8.1.1 Other Names

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

8.1.2 Classification

NEDD8-activating enzyme (NAE) inhibitor

8.1.3 Mode of Action

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

8.1.4 Description

White to off-white solid with an assay value of 96.0% to 103.0% (w/w) on an anhydrous basis. Acid dissociation constants of pKa1= 5.16 and = 8.81.

8.1.5 How Supplied

Takeda supplies and PMB distributes MLN4924 (Pevonedistat HCl) formulated as 10 mg/mL Concentrate for Solution for Infusion. Each single-use vial contains either 50 mg (5 mL) or 44 mg (4.4 mL) free base equivalent containing the following excipients: [redacted]

[redacted] The sterile solution is packaged in USP Type I glass vials with rubber stoppers (latex free), aluminum seals with plastic caps.

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

8.1.6 Preparation

Before use, bring MLN4924 (Pevonedistat HCl) vials to ambient room temperature (150 – 300 C / 590 – 860 F) for 15 minutes. Do not use a water bath to warm up the vials. Return vials to 20 – 80 C (360 – 460 F) storage if not used within 6 hours.

Use a 250 mL prefilled 5% Dextrose (D5W) or 0.9% Normal Saline (NS) IV bag:

- Remove excess volume from 250 mL D5W or NS prefilled IV bag
- Add the calculated dose (mL) of pevonedistat
- Final volume (250 mL) = drug + D5W or NS
- Do not shake; gently mix the IV solution by inverting the IV bag several times
- Inspect the IV solution to ensure it is clear and free of visible particles

Alternatively, a 250 mL empty IV bag can be used:

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

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

8.1.7 Storage

Store MLN4924 (Pevonedistat HCl) refrigerated at 20 – 80 C (360 – 460 F) in its original carton to protect from light.

If a storage temperature excursion is identified, promptly return MLN4924 (Pevonedistat HCl) to 20 – 80 C (360 – 460 F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

8.1.8 Stability

Stability studies are ongoing.

- The prepared IV solution is stable when stored at ambient room temperature up to 6 hours and must be administered within that time frame. Discard the IV bag if > 6 hours from the time of preparation.
- The prepared IV solution is stable when stored at 2 -- 8 C (36 – 46 F) up to 18 hours. The IV solution can be brought to ambient room temperature before administering to patient but must be used within 3 hours from the time it is removed from the refrigerator to completion of the IV infusion. Discard the IV bag if > 3 hours.

8.1.9 Dose Specifics

- Arm A, B: 50 mg/m^2 IV on days 1, 3, and 5 every cycle
- Arm B: 20 mg/m^2 IV on days 1, 3, and 5 every cycle

8.1.10 Route of Administration

Intravenous

8.1.11 Method of Administration

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

8.1.12 Potential Drug Interactions

In vitro, MLN4924 is metabolized mainly by hepatic CYP3A4/5 and to some extent by CYP2D6 (3%). CYP1A1 and 2J2 appear to be involved in extrahepatic metabolism, which may explain the lack of drug-drug interaction with CY3A4/5 inhibitors. This was demonstrated in an in vivo PK study where a moderate CYP3A inhibitor (e.g., fluconazole) and a strong CYP3A4 inhibitor (e.g., itraconazole, which is also a strong P-gp inhibitor) did not result in interactions when administered with pevonedistat. Therefore, drugs that are CYP3A/P-gp inhibitors can be used in patients receiving pevonedistat. **Use of strong CYP3A inducers (e.g., rifampin, phenytoin, St. John's wort) with MLN4924 is prohibited.**

In vitro, MLN4924 is **not** an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC_{50} > 100 µM and Ki >50 µM) but is a weak inhibitor of CYP2B6 and 2C8 (IC50 = 97.6 and 23.1 µM, respectively). MLN4924 causes concentration-dependent decreases in CYP1A2, 2B6, and 3A4/5 mRNA expression and/or activities but is not expected to affect the PK of CYP1A2, 2B6 or 3A4/5 substrates.

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

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

8.1.13 Availability

Pevonedistat will be supplied by Takeda and distributed by Pharmaceutical Management Branch (PMB).

8.1.14 Side Effects

See Section 5.3 for the Comprehensive Adverse Events and Potential Risks list (CAEPR) for Pevonedistat HCl (MLN4924, NSC793435).

8.2 Carboplatin

8.2.1 Other Names

Paraplatin®

8.2.2 Classification

Carboplatin (carboplatin injection) (platinum, diammine[1,1-cyclobutanedicarboxylato(2-)-O,O']-, (SP-4-2)) is a platinum coordination compound, used as an anti-neoplastic agent. It is a second-generation tetravalent organic platinum compound. It is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

8.2.3 Mode of Action

Like cisplatin, carboplatin binds to DNA, thereby inhibiting DNA synthesis, in a cell cycle nonspecific manner. Carboplatin must first undergo activation to produce antineoplastic activity. Bidentate carboxylate ligands of carboplatin are displaced by water forming (aquation) positively charged platinum complexes, which bind to nucleophilic sites in DNA, such as the O-6 position on guanine. Carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Intrastrand crosslinks result from the formation of adducts between the activated platinum complexes of the drug and the N-7 atom (not exclusively) atom on guanine to produce 1,2 intrastrand links between adjacent guanine molecules, between neighboring guanine and adenosine molecules, or between neighboring guanine molecules. Interstrand cross-linking within the DNA helix also occurs. Platinum adducts may inhibit DNA replication, transcription and ultimately cell division.

8.2.4 Storage and Stability

Store intact vials at room temperature at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light. Further dilution to a concentration as low as 0.5 mg/mL is stable at room

temperature (25°C) for 8 hours in NS or D_5W. Stability has also been demonstrated for dilutions in D_5W in PVC bags at room temperature for 9 days; however, the manufacturer recommends use within 8 hours due to lack of preservative. Multidose vials are stable for up to 14 days after opening when stored at 25°C (77°F) following multiple needle entries.

8.2.5 Dose Specifics

- Arm B: Carboplatin at AUC 5 IV on day 1 of every 21 day cycle

Calvert Formula for Carboplatin (AUC) Dosing

Total dose (mg) = target AUC (in mg/mL/minute) * [GFR (in L/minute) + 25]

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance.

Glomerular Filtration Rate (GFR) Estimation: Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula:

Males: $\frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$

Females: Estimated creatinine clearance for males x 0.85

Round up any creatinine ≤ *0.7 mg/dL, to 0.7 mg/dL*

With the Calvert formula, the total (final) dose of carboplatin is calculated in mg, not mg/m^2.

8.2.6 Preparation

Manufacturer's labeling states solution can be further diluted to concentrations as low as 0.5 mg/mL in NS or D_5W; however, most clinicians generally dilute dose in either 100 mL or 250 mL of NS or D_5W. Concentrations used for desensitization vary based on protocol. Hazardous agent; use appropriate precautions for handling and disposal. Needles or IV administration sets that contain aluminum should not be used in the preparation or administration of carboplatin; aluminum can react with carboplatin resulting in precipitate formation and loss of potency.

8.2.7 Route of Administration

Intravenous

8.2.8 Incompatibilities

Amphoterecin B chloesteryl sulfate complex. Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

8.2.9 Availability

Carboplatin (Bristol-Myers Oncology Division) is commercially available in 50, 150, and 450 mg vials.

8.2.10 Side Effects

Please refer to the commercial package insert.

8.2.11 Nursing/Patient Implications

- Monitor CBC and platelet count; nadir occurs at approximately day 21 with recovery by day 28-30.
- Premedicate with antiemetics—evaluate effectiveness. Ondansetron (or other 5HT3 antagonist) and dexamethasone are required.
- Monitor fluid status—maintain adequate hydration. Pre- and post-treatment hydration may be administered per institutional standards.
- Assess skin/mucous membranes.
- Assess for signs of peripheral neuropathy—coordination, sensory loss.

8.2.12 References

1. Calvert AH, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 7:1748-1756.
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8.3 Paclitaxel

8.3.1 Other Names

Taxol, NSC 673089.

8.3.2 Classification

Antimicrotubule agent.

8.3.3 Mode of Action

Promotes microtubule assembly and stabilizes tubulin polymers by preventing their depolarization, resulting in the formation of extremely stable and nonfunctional microtubules, and consequently inhibition of many cell functions.

8.3.4 Storage and Stability

The intact vials are stored under refrigeration. Freezing does not adversely affect the product. Solutions diluted to a concentration of 0.3 to 1.2 mg/mL in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution are stable for up to 27 hours when stored at room temperature and normal room light.

8.3.5 Dose Specifics

- Arm B: Paclitaxel 175mg/m^2 IV on day 1 of each 21 day cycle.

8.3.6 Preparation

The concentrated solution must be diluted prior to use in normal saline, 5% dextrose, 5% dextrose and normal saline, or 5% dextrose in Ringer's solution to a concentration of 0.3 -1.2 mg/mL. Solutions exhibit a slight haze, common to all products containing non-ionic surfactants. Glass, polypropylene, or polyolefin containers and non-PVC-containing (nitroglycerin) infusion sets should be used. A small number of fibers (within acceptable limits established by the USP) have been observed after dilution. Therefore, a hydrophilic 0.22 micron in-line filter should be used. Analyses of solutions filtered through IVEX-2 and IVEX-HP (Abbott) 0.2 micron filters showed no appreciable loss of potency.

Solutions exhibiting excessive particulate formation should not be used.

8.3.7 Route of Administration

Intravenous.

8.3.8 Incompatibilities

Avoid the use of PVC bags and infusion sets due to leaching of DEHP (plasticizer). Ketoconazole may inhibit paclitaxel metabolism, based on *in vitro* data.

8.3.9 Availability

A concentrated solution of 6 mg/mL in polyoxyethylated castor oil (Cremophor EL) 50% and dehydrated alcohol 50% is commercially available in 5 mL vials.

8.3.10 Side Effects

Please refer to the commercial package insert

8.3.11 Nursing/Patient Implications

- Monitor CBC and platelet count prior to drug administration.
- Symptom management of expected nausea, vomiting, and stomatitis.
- Monitor for and evaluate abdominal pain occurring after paclitaxel administration (especially in severely neutropenic patients and in those receiving G-CSF) due to the risk of ischemic and neutropenic enterocolitis.
- Advise patients of possible hair loss.
- Cardiac monitoring for assessment of arrhythmias in patients with serious conduction abnormalities.
- Monitor liver function tests.
- Advise patient of possible arthralgias and myalgias which may occur several days after treatment. Monitor for symptoms of peripheral neuropathy.
- Monitor for signs and symptoms of hypersensitivity reactions. Insure that the recommended premedications have been given. Premedications (diphenhydramine, steroids, and H2 blocker) appear to reduce the incidence and severity of hypersensitivity

reactions but do not provide complete protection. Emergency agents (diphenhydramine and epinephrine) should be available.

- Evaluate IV site regularly for signs of infiltration. It is not known if paclitaxel is a vesicant; however, the CremophorEL vehicle for this drug can cause tissue damage.
- In-line filtration with a 0.22 micron filter should be used.

8.3.12 References

Rowinsky EK, Casenave LA, Donehower RC. Taxol: A novel investigational microtubule agent. J Natl Cancer Inst 1990; 82:1247-1259.

Gregory RE, DeLisa AF. Paclitaxel: A new antineoplastic agent for refractory ovarian cancer. Clin Pharm 1993; 12: 401-415.

Rowinsky EK, Eisenhauer EA, Chaudry V, *et al.* Clinical toxicities encountered with paclitaxel. Semin Oncology 1993; 20:1-15.

Walker FE. Paclitaxel: Side effects and patient education issues. Semin Oncology Nurs 1993; 9(suppl 2):6-10.

9. Statistical Considerations

This trial is a randomized phase II study evaluating each arm separately for an efficacy signal. The primary endpoint is objective response (complete or partial response by RECIST v1.1). Secondary endpoints are to report on PFS, toxicity, disease control rate and overall survival. For the primary ORR endpoint, the null (uninteresting) proportion is 10% and the target proportion that would lead to further study is 30% (alternative). Within each arm there will be a two-stage minimax design such that 16 eligible and treated patients will be evaluated at the first stage in each arm (33 across the two arms to allow for ineligibility). Accrual will pause while awaiting the results of the first stage analysis as the accrual rate is expected to be on the order of 5 patients per month. If at least 2 patients in an arm achieve response, the arm will move to the second stage and recruit 9 additional eligible and treated patients. Success of an arm will be achieved (reject the null hypothesis) if 5 or more patients have a response. Within each arm there is a 51.5% chance of stopping at the first stage under the null hypothesis and each arm has type I error of no more than 10% and 90% power. If both arms move to their respective second stages, the recommended arm for further testing will be decided based on the overall profile of efficacy and safety.

A total of up to 52 patients will be enrolled if the study moves to the second stage in both arms (33 at the first stage and 19 at the second stage). Accrual has been increased by 2 patients to allow for ineligibility.

With 25 eligible and treated patients in an arm, there is at least 80% probability of observing a rare adverse event with true probability of 0.065 or higher and a 90% confidence interval for any binomial parameter will be no wider than 36%.

Correlative Endpoints

Immunohistochemistry for NEDD8, NAE1 and UBC12 will be performed on FFPE pre-trial diagnostic tissue. Biomarker quantification will be calculated as a continuous variable (mean optical density) and also as ordered categories (ex. 0, 1+, 2+, or 3+). Biomarker quantification will then be correlated with treatment response. All correlative studies are considered exploratory as power will be limited with 25 patients per arm. For example, in order to have 80% power to detect a difference in objective response between two groups equally split via a correlative biomarker, the true difference in response between the group would need to be on the order of 50%. Hence the study is not expected provide any definitive evidence, rather they will be hypothesis generating.

Descriptive statistics will primarily be generated to summarize the correlative data. For continuous variables, descriptive statistics may include the number of subjects (n), mean, standard deviation, median, minimum, and maximum; frequencies and percentages may be displayed for categorical data. Data summaries will be presented by arm. Statistical significance will be determined by students' t-test for normally distributed data. If data distributions are not normal, non-parametric methods will be used (Wilcoxon rank sum test).

Safety Monitoring

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.1 Gender and Ethnicity

Based on previous data from PrECOG study 0204 (74 patients) the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	2	4
Not Hispanic or Latino	29	19	48
Ethnic Category: Total of all subjects	**31**	**21**	**52**

Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	0	1
Black or African American	2	2	4
Native Hawaiian or other Pacific Islander	0	0	0
White	28	19	47
Racial Category: Total of all subjects	**31**	**21**	**52**

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Specimen Submissions

Tumor tissue specimens should be submitted for use in the laboratory correlative study described in Section 11. Residuals from the analysis will be retained for unknown future research for patients that answer "Yes" to "I agree that my samples and related health information may be kept in a biobank for use in future health research"

All specimens must be labeled with the ECOG-ACRIN protocol number, the patient's initials and ECOG-ACRIN sequence number, the collection date, and the type of sample. For pathology materials, it is strongly recommended that full patient names be provided.

All specimens must be logged and tracked via the ECOG-ACRIN Sample Tracking System (STS) Web Application (Section 10.4) and submitted with an STS generated shipping manifest.

10.1 Collection and Submission Schedule

See Section 7.2 for a table summarizing the submission requirements.

10.1.1 Tissue Submissions

Specimens are to be submitted within 4 weeks following registration to the trial.

Guidelines for pathologists are provided in Appendix I.

10.1.1.1 Pre-Trial Diagnostic Tissue (**Mandatory if available)**:

Please submit fixed, paraffin-embedded tumor tissue blocks.

NOTE: If blocks are not available for submission, the following alternative is to be submitted: 1 H&E (from the source block), 1-2 core punches (4 mm minimum) and 20 unstained slides (5 microns thick). Slides, including the H&E, are to be numbered consecutively in the order cut.

10.1.1.2 Forms

The relevant pathology and surgical reports must accompany all tissue submissions:

- Copy of the diagnostic or surgical Pathology Report
- Other Immunologic and cytologic reports
- STS generated shipping manifest for all submitted tissue

10.2 Shipping Procedures

Submissions to ECOG-ACRIN Central Biorepository and Pathology Facility

The pathology materials are to be submitted within 4 weeks following registration to the trial. Tissue samples are to be shipped at ambient (use a cool pack in warm weather).

Shipping manifest generated from the ECOG-ACRIN STS system must accompany the samples.

Access to the shipping account for specimen shipments to the ECOG-ACRIN CBPF at MD Anderson can now only be obtained by logging into fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Blvd
Houston, TX 77030
Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
Fax: 713-563-6506

10.3 Use of Specimens in Research

Specimens submitted will be processed to maximize their utility for current and future research projects and may include, but not limited to, extraction of plasma, serum, DNA and RNA.

The appropriate materials will be distributed to investigators for research studies.

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined reviews and research studies, will be retained in an ECOG-ACRIN-designated central repository. For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility. Specimens will be de – identified prior to distribution for any approved research products.

If future use is denied or withdrawn by the patient, the samples will be removed from consideration for use in any future study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

10.4 ECOG-ACRIN Sample Tracking System

It is **required** (barring special circumstances) that all samples submitted to the E-A CBPF on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). As of June 2007, the software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the samples required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html. Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest must be generated and shipped with all sample submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu .

Study Specific Notes:

If the STS is unavailable, the Generic Specimen Submission Form (#2981) is to be used as a substitute for the STS shipping manifest. The completed form is to be faxed to the receiving laboratory the day the samples are shipped. Indicate the appropriate Lab on the submission form:

- ECOG-ACRIN CBPF

Retroactively enter all specimen collection and shipping information when STS is available.

10.5 Sample Inventory Submission Guidelines

Inventories of all samples submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the will be submitted by the laboratory to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Specimen Analyses: Research Studies

Pre-trial diagnostic tissue is required to be submitted for the following research study. This study will be performed at the University of Wisconsin, under the direction of Dustin Deming, MD.

11.1 Immunohistochemistry for NEDD8, NAE1 and UBC12

Historic histological slides will be used to compare the efficacy of pevonedistat with the presence of overexpression of the neddylation pathway. The Deming laboratory has significant experience with immunohistochemistry (IHC) techniques. Immunohistochemical studies will be performed on formalin-fixed/paraffin-embedded archival tumor tissue examining levels of NEDD8, NAE1 and UBC12. Biomarker quantification will be calculated as a continuous variable (mean optical density) and also as quartiles (ex. 0, 1+, 2+, or 3+). Biomarker quantification will then be correlated with treatment response. Additionally, the molecular profile obtained as part of standard of care will be compared to the expression of these markers using a regression analysis. 10 slides will be provided by the biobank to the investigating laboratory for these analyses.

11.2 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator. The quarterly cut-off dates are March 31, June 30, September 30, and December 31. Data is due at the ECOG-ACRIN Operations Office - Boston 1 week after these cut-off dates

12. Electronic Data Capture

Please refer to the **EA2187** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Complete reporting consists of Patient Demographics, Baseline Abnormalities, On/Off Treatment/Study Status, Treatment/Course/Dosing information, Adverse Events, Late Adverse Events, and Response data as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (https://ctep.cancer.gov/protocolDevelopment/dmu.html).

NOTE: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

14. References

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Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Guidelines for Submission of Pathology Materials

The following items should always be included when submitting pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF):

- Institutional Surgical Pathology Report
- Pathology materials
- ECOG-ACRIN Sample Tracking System (STS)-Generated Shipping Manifest

Instructions:

1. Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, will expedite any required communications with the institution (including site pathologists).
2. Pathology materials required for research:
   - FFPE Pre-Trial Diagnostic, Mandatory (if available, no new biopsy required)

   Pre-trial diagnostic specimens are to be submitted within 4 weeks following registration to the trial.

NOTE: If blocks are not available for submission, the following alternative is to be submitted: 1 H&E (from the source block), 20 unstained slides (5 microns thick) and 1-2 core punches (4 mm minimum). Slides, including the H&E, are to be numbered consecutively in the order cut.

NOTE: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

3. A copy of the ECOG-ACRIN STS Sample Tracking System manifest or relevant sample submission documents should be kept for your records.
4. Copies of the pathology, cytology and procedure reports associated with the submitted tissue must be submitted. Double-check that ALL required forms, reports and pathology samples are included in the package.
5. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
   1515 Holcombe Blvd
   Houston, TX 77030
   Phone: Toll Free 1-844-744-2420 (713-745-4440 Local or International Sites)
   Fax: 713-563-6506
   Email: eacbpf@mdanderson.org

If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility.

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: Submission of Pathology Materials for EA2187: A Phase 2 Study of Pevonedistat in Combination with Carboplatin and Paclitaxel in Advanced Intrahepatic Cholangiocarcinoma

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for laboratory studies.

Keep a copy of the submission for your records and return any relevant completed forms, the surgical pathology report(s), the slides and/or blocks and any other required material to the Clinical Research Associate (CRA). The CRA will forward all required pathology material to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Central Repository for future studies per patient consent. Paraffin blocks will be returned upon request for purposes of patient management.

Please note: Since blocks are being used for laboratory studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

This review will be retrospective and will not impact patient participation in EA2187.

If you have any questions regarding this request, please contact the Central Biorepository and Pathology Facility at (1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

A Phase 2 Study of Pevonedistat in Combination with Carboplatin and Paclitaxel in Advanced Intrahepatic Cholangiocarcinoma

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

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Appendix III

CRADA/CTA

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

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

   ncicteppubs@mail.nih.gov

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

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Appendix IV

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

A Phase 2 Study of Pevonedistat in Combination with Carboplatin and Paclitaxel in Advanced Intrahepatic Cholangiocarcinoma

Appendix V

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on pevonedistat, or within 28 days of the female patient's last dose of pevonedistat must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

For this study, a pregnancy, suspected pregnancy (including a positive or inconclusive pregnancy test) must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm the pregnancy requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status in CTEP-AERS accessed via Medidata Rave
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.

- *It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* and separate CTEP-AERs report should be initiated (via Medidata Rave) reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

For this study, it must initially be reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm the pregnancy loss requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The pregnancy loss must be reported as a Grade 4 "*Pregnancy Loss*" under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A pregnancy loss should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to Pevonedistat must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the event is entered into Rave, the Rules engine on the Expedited Reporting Evaluation Form will confirm the neonatal death requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The neonatal death must be reported as a Grade 4 "*Death neonatal*" under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf).

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Appendix VI

Patient Drug Interactions Handout and Wallet Card

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

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

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

These are the things that your healthcare providers need to know:

MLN4924 (pevonedistat) interacts with certain specific enzyme in your liver or other tissue like the gut and certain transport proteins that help move drugs in and out of cell.

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

These are the things that you need to know:

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

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

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

Table Concomitant Medications Excluded During the Study

Therapy	Comment/Exceptions
Acetaminophen and acetaminophen-containing products	Agents such as acetaminophen and acetaminophen-containing compounds may be used judiciously and should not exceed a dose of 2 g of acetaminophen in a 24 hour period.
Systemic antineoplastic therapy, except for hydroxyurea	
Clinically significant metabolic enzyme inducers	Excluded IN THE STUDY In Arm B ONLY: Avoid the concomitant use of inhibitors or inducers of CYP2C8 and CYP3A4
Known BCRP inhibitors (ie, cyclosporine)	Excluded **but limited use is permitted only if clinically necessary and no suitable alternative exists.** The patient may receive the BCRP inhibitor from 24 hours after the last pevonedistat dose until 72 hours before the next pevonedistat dose. For example, if a patient receives pevonedistat on a Monday (Day 1), Wednesday (Day 3), Friday (Day 5) schedule, then the BCRP inhibitor may be administered from the Saturday after the Day 5 dose (Day 6) up to the Friday (Day 26) before the Monday dose of the next cycle. Avoid the concomitant use of nephrotoxic drugs IN Arm B of the study
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,

Version JAN/2019

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE **EMERGENCY INFORMATION**	NIH NATIONAL CANCER INSTITUTE	NIH NATIONAL CANCER INSTITUTE **DRUG INTERACTIONS**	NIH NATIONAL CANCER INSTITUTE
Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.	Tell your doctors **before** you **start** or **stop** any medicines. **Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!**	**Carry this card with you at all times** MLN4924 (pevonedistat) interacts with enzymes in your liver or other tissue like the gut, transport proteins that help move drugs in and out of cells and must be used very carefully with other medicines.	
Patient Name: **Diagnosis:** **Study Doctor:** **Study Doctor Phone #:** **NCI Trial #:** **Study Drug(S):** MLN4924 (pevonedistat)	**Use caution and avoid the following drugs if possible:** St. John's Wort, grapefruit or grapefruit juice	Your healthcare providers should be aware of any medicines that are strong inducers of CYP3A. Drugs that are CYP3A inducers (e.g., rifampin, St. John's Wort) are not allowed. **Before prescribing new medicines**, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor. Version JAN/2019	
For more information: 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov	**For more information:** 1-800-4-CANCER cancer.gov | clinicaltrials.gov

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Appendix VII

Formula to Estimate Renal Function Using Serum Creatinine

Formulas to estimate renal function using serum creatinine provided by the NCI's Investigational Drug Steering Committee (IDSC) Pharmacological Task Force in table below.

1. Estimated glomerular filtration rate (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (Levey et al., 2009).

Formulae:

Race and Sex	Serum Creatinine (SCr), *µmol/L (mg/dL)*	Equation
Black		
Female	≤ 62 (≤ 0.7)	$GFR = 166 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	> 62 (> 0.7)	$GFR = 166 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤ 80 (≤ 0.9)	$GFR = 163 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	> 80 (> 0.9)	$GFR = 163 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$
White or other		
Female	≤ 62 (≤ 0.7)	$GFR = 144 \times (SCr/0.7)^{-0.329} \times (0.993)^{Age}$
	> 62 (> 0.7)	$GFR = 144 \times (SCr/0.7)^{-1.209} \times (0.993)^{Age}$
Male	≤ 80 (≤ 0.9)	$GFR = 141 \times (SCr/0.9)^{-0.411} \times (0.993)^{Age}$
	> 80 (> 0.9)	$GFR = 141 \times (SCr/0.9)^{-1.209} \times (0.993)^{Age}$

SCr in mg/dL; Output is in mL/min/1.73 m^2 and needs no further conversions.

2. eGFR using the Modification of Diet in Renal Disease (MDRD) Study (Levey et al., 2006).

   175 x SCr–1.154 × age–0.203 × 0.742 (if female) × 1.212 (if black)
   Output is in mL/min/1.73 m^2 and needs no further conversions.

3. Estimated creatinine clearance (ClCr) by the Cockcroft-Gault (C-G) equation (Cockcroft and Gault, 1976).

$$CLcr\ (mL/min) = \frac{[140 - age\ (years)] \times weight\ (kg)}{72 \times serum\ creatinine\ (mg/dL)} \{\times 0.85\ for\ female\ patients\}$$

   Followed by conversion to a value normalized to 1.73 m^2 with the patient's body surface area (BSA).

References:

1. Levey, A.S., L.A. Stevens, C.H. Schmid, *et al*. (2009). A new equation to estimate glomerular filtration rate. *Ann Inter Med*. 150:604-612.
2. Levey, A.S., J. Coresh, T. Greene, *et al*. (2006). Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 145:247-254.
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