DATE: December 20, 2021

TO: CTEP Protocol and Information Office

FROM: Ticiana Leal, MD

SUBJECT: Amendment 10 to update the PI's contact information.

SUMMARY OF CHANGES – Protocol

I. Response to Dr. Kem's Notice to Principal Investigators dated 8/12/21:

#	Section	Change
1.	Header	Updated version date.
2.	Title Page	Updated Dr. Leal's contact information at Emory University. Removed Kasey and Claire as study contacts. Added amendment version and date.

SUMMARY OF CHANGES – Consent Form

#	Section	Change
1.	Header	Updated version date.

NCI Protocol #: 10266

Local Protocol #: NCI10266

ClinicalTrials.gov Identifier: NCT03965689

TITLE: A Phase 2 Study of MLN4924 (pevonedistat) in Combination with Carboplatin and Paclitaxel in Advanced NSCLC Previously Treated with Immunotherapy

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LAO-CT018 / Yale University Cancer Center LAO
LAO-MA036 / Dana-Farber - Harvard Cancer Center LAO
LAO-MD017 / JHU Sidney Kimmel Comprehensive Cancer Center LAO
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LAO-NC010 / Duke University - Duke Cancer Institute LAO
LAO-NJ066 / Rutgers University - Cancer Institute of New Jersey LAO
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CATCHUP / Creating Access to Targeted Cancer Therapy for Underserved Populations

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NCI-Supplied Agent: MLN4924 (pevonedistat) HCL (NSC 793435)

Other Agent(s): Carboplatin (NSC 241240), Commercial
Paclitaxel (NSC 673089), Commercial

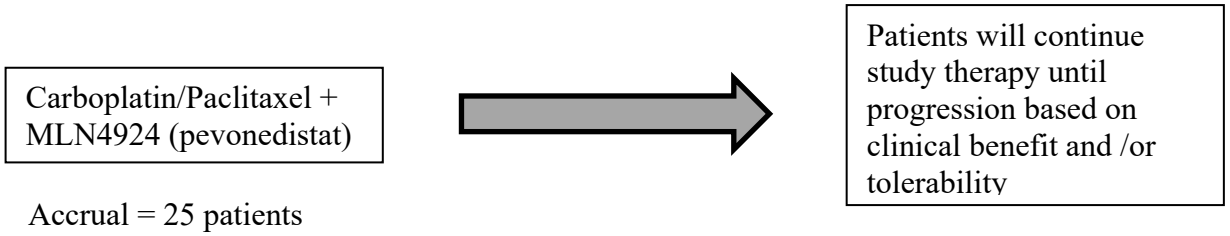
[redacted]

IND Sponsor: DCTD, NCI

Protocol Type / Version # / Version Date:
Original / December 28, 2018
Revision 1 / March 7, 2019
Revision 2 / April 4, 2019
Revision 3 / May 1, 2019
Revision 4b / June 17, 2019
Revision 4a / June 21, 2019
Revision 5 / August 7, 2019
Revision 6 / September 16, 2019
Revision 7 / November 19, 2019
Revision 8 / May 14, 2020
Amendment 4 / July 13, 2020
Amendment 5 / September 5, 2020
Amendment 6 / October 5, 2020
Amendment 7 / March 3, 2021
Amendment 8 / June 24, 2021
Amendment 9 / August 23, 2021
Amendment 10 / December 20, 2021

SCHEMA

Phase 2 single-arm study



Accrual = 25 patients

Treatment Plan:

Patients will receive at least 4 cycles of therapy. Treatment will be continued until progressive disease, unacceptable toxicity or patient desire to discontinue study therapy. At any time after 4 cycles of combination therapy, the treating physician is given discretion whether to continue with

a) carboplatin, paclitaxel, and MLN4924 (pevonedistat), or b) continue carboplatin and MLN4924 (pevonedistat) without paclitaxel, or c) observe the patient on study. All patients will be followed for the duration of study and until resolution or stabilization of any adverse effects related to study therapy. If the patient is continued on a) or b), subsequent change to c) at later timepoints is also allowed.

- MLN4924 (pevonedistat): 20 mg/m^2 intravenous (IV), Days 1, 3, 5
- Carboplatin: Area under the curve (AUC) = 5 IV, Day 1
- Paclitaxel: 175 mg/m^2 IV, Day 1

Cycle = 3 weeks (21 days)

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objective

1.1.1 To determine the overall response rate (ORR) of patients with advanced non-small cell lung cancer (NSCLC) treated with MLN4924 (pevonedistat) in combination with carboplatin and paclitaxel.

1.2 Secondary Objectives

1.2.1 To estimate the progression-free survival (PFS) of patients with advanced NSCLC treated with MLN4924 (pevonedistat) in combination with carboplatin and paclitaxel.

1.2.2 To estimate the overall survival (OS) of patients with advanced NSCLC treated with MLN4924 (pevonedistat) in combination with carboplatin and paclitaxel.

1.2.3 To evaluate the safety profile of MLN4924 (pevonedistat) in combination with carboplatin and paclitaxel.

1.3 Correlative Objectives

1.3.1 To evaluate expression of nuclear factor-erythroid 2 p45-related factor 2 (NRF2) target genes NAD(P)H: quinone oxidoreductase1 (*NQO1*) and the cysteine/glutamate antiporter solute carrier family 7 member 11 (*SCL7A11)*.

1.3.2 To determine expression of pharmacodynamic markers induced by neural precursor cell expressed developmentally downregulated protein 8 (NEDD-8) activating enzyme (NAE) inhibition: cyclic AMP-dependent transcription factor (*ATF3*), β_2 microglobulin (*B2M*), glutamate-cysteine ligase regulatory subunit (*GCLM*), glutathione-disulfide reductase (*GSR*), DNA-3-methyladenine (*MAG1*), ribosomal protein lateral stalk subunit P0 (*RPLPO*), sulfiredoxin-1 (*SRXN1*), thioredoxin reductase 1 (*TXNRD1*), and ubiquitin-conjugating enzyme (*UBC*).

1.3.3 To perform qualitative assessment of tumor NAE1 and ubiquitin-conjugating enzyme E2 M (UBC12) protein expression at baseline.

1.3.4 To assess circulating tumor cells (CTCs) for DNA damage repair pathway alterations (*i.e.,* γH2AX induction, RAD51).

1.3.5 To evaluate pharmacokinetic (PK) parameters of MLN4924 (pevonedistat) when given in combination with paclitaxel and carboplatin.

2. BACKGROUND

2.1 Study Diseases

Lung cancer, one of the leading causes of all-cancer mortality, can be divided into two subcategories based on histological classification – NSCLC and small-cell lung cancer. NSCLC accounts for nearly 85% of all lung cancers and is the leading cause of cancer-related mortality in the United States with an estimated 155,870 deaths from lung cancer in 2017 (American Cancer Society, 2017).

The current standard of care for non-squamous NSCLC depends in large part on whether actionable mutations can be identified and lead to an opportunity for an effective targeted treatment option. Initial biopsy specimens or plasma are sent for genomic analysis to identify activating epidermal growth factor receptor (EGFR) mutations in exon 19 and 21 or gene rearrangements in anaplastic lymphoma kinase (ALK) or ROS1 and BRAF (B-Raf proto-oncogene). Tumors which harbor sensitizing EGFR mutations are responsive to a number of EGFR tyrosine kinase inhibitors (TKI) including osimertinib, erlotinib, gefitinib, and afatinib, and use of an EGFR TKI is recommended in the first line setting. ALK translocations should be treated with an ALK TKI in the first line setting such as alectinib, ceritinib or crizotinib. ROS1 rearrangements can be treated with crizotinib in the first line setting, and BRAF mutations can be effectively treated with combination of trametinib and dabrafenib (Ettinger *et al.,* 2018). However, the same progress has not been achieved in treating patients with advanced squamous cell lung cancer where there are no approved targeted therapy options.

The majority of patients with advanced NSCLC do not have a driver mutation. For these patients with advanced NSCLC, the standard of care treatment options in the front-line setting include immunotherapy with pembrolizumab for patients whose tumor express PD-L1 ≥ 50% (Reck *et al*., 2016). The combination of immunotherapy with chemotherapy has also led to improved outcomes compared to platinum-based chemotherapy and led to recent approvals for patients, independent of PD-L1 expression: platinum/pemetrexed/pembrolizumab in the non-squamous population (Gandhi *et al*., 2018) and platinum/taxane/pembrolizumab in the squamous population (Paz-Ares *et al*., 2018).

For a disease that had a five-year survival rate of only 5% for advanced stages, the addition of immunotherapy has improved that rate to 16 percent (Gettinger *et al.,* 2018). While there have been significant improvements in patient outcomes and survival with the introduction of immunotherapy and molecularly targeted agents for patients with NSCLC, only a subset of patients respond and have prolonged survival (Temel *et al.,* 2018*)*.

In the second-line setting, the mainstay of therapy has previously been single-agent immunotherapy with PD-1/PD-L1 inhibitors following progression on platinum-based doublet chemotherapy. However, with the increasing use of immunotherapy in combination with platinum chemotherapy in the front-line, this is no longer an effective or recommended approach. The second-line treatment option will once again include docetaxel +/- ramucirumab, a monoclonal antibody against the vascular endothelial growth factor receptor 2 (VEGFR2). The latter treatment is associated with modest benefit in OS and potential significant toxicity (Garon

et al., 2014). Other regimens in this setting include gemcitabine, or pemetrexed in patients with non-squamous histology who have not received it previously.

Therefore, even in this era of immunotherapy and precision medicine, cytotoxic chemotherapies remain an essential therapeutic option for patients with advanced NSCLC in the course of their disease trajectory (Hellmann *et al*., 2016). Development of combination strategies after development of resistance to front-line immunotherapy is an area of unmet need. There is a continued clear need to develop novel therapeutic strategies, enhancing the efficacy of cytotoxic chemotherapy regimens and to investigate predictive biomarkers in NSCLC.

One developing novel therapeutic strategy in lung cancer considers the molecular pathway of the ubiquitin (Ub)/proteasome system (UPS), which is responsible for a variety of cellular functions via protein degradation and a potential promising oncological target (Ji *et al*., 2017; Zhou *et al*., 2017).

2.1.2. Neddylation pathway

The UPS controls a broad array of cellular functions via protein degradation that mediate cell growth and survival, cellular signaling, and transcription factor regulation (Wu and Yu, 2016). The efficacy of proteasome inhibitors such as bortezomib and carfilzomib in multiple myeloma, for example, has validated the UPS as a rational target for cancer therapy (Esseltine and Mulligan, 2012). The therapeutic index of proteasome inhibitors may be improved through selective inhibition of a sub-component of the UPS, such as the neddylation pathway, which is responsible for about 20% of protein degradation (Soucy *et al*., 2009).

Ub conjugation via covalent linkage to a protein tags it for degradation by a proteasome. Ubiquitination 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-ligasing (E3). A subgroup of E3 ligases, which include Cullin RING ligases (CRL), are responsible for approximately 20% of cellular proteins labeled for degradation (Soucy *et al*., 2009). CRL substrates include regulators of cell cycle progression, apoptosis, DNA damage response, and signaling transduction. This subgroup of E3 ligases are regulated via a Ub-like ligand, NEDD8, via covalent conjugation. As with Ub, neddylation to CRL occurs in three enzymatic steps that include NEDD8-activating enzyme (NAE1), E2 conjugation (UBC12), and an E3 ligase. Given the downstream substrates of CRLs include a number of oncoproteins and tumor suppressors, inhibiting neddylation is a promising oncologic therapeutic target.

Up-regulation of the neddylation pathway has been shown in several malignancies including melanoma, intrahepatic cholangiocarcinoma, and NSCLC (Gao *et al*., 2014; Cheng *et al*., 2104; Li *et al.,* 2014). In a study evaluating expression of NEDD8-activating enzyme (NAE) (E1) and NEDD8-conjugating enzyme (E2) expression and global-protein neddylation, both squamous cell and adenocarcinoma NSCLC tumors consistently demonstrated overactivation of the entire neddylation pathway. Moreover, higher expression of neddylation pathway was associated with

poor overall survival. To validate the hypothesis that overactivation of the neddylation pathway may serve as a therapeutic target, Li *et al.* evaluated the efficacy of neddylation inhibition by adding MLN4924 (pevonedistat) in human and murine lung cancer cells and demonstrated statistically significantly suppressed proliferation, survival, migration, and motility of lung cancer cells in vitro and tumor formation and metastasis *in vivo* (Li *et al*., 2014)

2.2 CTEP IND Agent

2.2.1 MLN4954 (pevonedistat)

MLN4924 (pevonedistat) (also known as TAK-924 and MLN4924) is a first-in-class, small molecule inhibitor of neural precursor cell expressed, developmentally down-regulated 8 (NEDD8)-activating enzyme (NAE) under development for the treatment of malignancies (Investigator's Brochure, 2018). The NEDD8 conjugation (neddylation) pathway is responsible for much of the regulated protein turnover in the cell (Podust *et al.*, 2000; Read *et al.*, 2000), which is similar to the ubiquitin-proteasome system (UPS). However, UPS is known to regulate a myriad of processes in eukaryotic cells, whereas only a limited number of neddylation substrates have been described to date. For example, Velcade® (bortezomib) for Injection, a drug that acts by inhibiting the 26S proteasome, has proven utility in the treatment of multiple myeloma and mantle cell lymphoma (Velcade Package Insert, 2014). Therefore, it is anticipated that other compounds directed against different components of the UPS and/or the NEDD8 conjugation pathway may prove useful in the treatment of malignancies.

NAE, an E1 ligase, is an essential component of the NEDD8 conjugation pathway, which initiates the neddylation of protein substrates (Investigator's Brochure, 2018; Podust *et al.*, 2000; Read *et al.*, 2000). Specifically, NEDD8 conjugation to Cullin-RING ubiquitin E3 ligases (CRLs) is necessary for their activity. The ligases in the NEDD8 conjugation pathway control the timely neddylation of many substrate proteins with important roles in cell cycle progression and signal transduction. The ubiquitination/neddylation of proteins targets them for proteasomal degradation. These cellular processes are relevant to tumor cell growth, proliferation, and survival. As such, inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers by inhibiting the degradation of a subset of proteins that are regulated by the proteasome. In nonclinical studies, treatment of cells with MLN4924 (pevonedistat) results in the accumulation of CRL substrates, followed by a DNA damage response and cell death.

2.2.1.1 Preclinical Experience with MLN4924 (pevonedistat)

MLN4924 (pevonedistat) is a potent and selective inhibitor of NAE activity (Investigator's Brochure, 2018). MLN4924 (pevonedistat) was at least 300- and 1800-fold more selective for NAE than for the closely related ubiquitin-activating enzyme and SUMO activating enzyme, respectively. MLN4924 (pevonedistat) treatment of cultured tumor cells resulted in growth inhibition of a wide variety of cell lines derived from acute leukemias, lymphomas, multiple myeloma, and a range of solid tumor types. Changes in protein levels observed in cultured cells treated with MLN4924 (pevonedistat) were consistent with the inhibition of NAE, in particular, a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CRL substrates, including Nrf-2, and chromatin-licensing and DNA-replication factor-1 (Cdt-1). In

most cell lines evaluated, NAE inhibition by MLN4924 (pevonedistat) led to DNA re-replication and accumulation of cells in the S phase of the cell cycle, resulting in DNA damage and subsequent cell death through apoptosis (Soucy *et al.*, 2009; Lin *et al.*, 2010; Milhollen *et al.*, 2011). When administered in combination with the hypomethylating agents, azacitidine and decitabine, MLN4924 (pevonedistat) demonstrated synergistic activity in acute myeloid leukemia (AML) cell lines. MLN4924 (pevonedistat) demonstrated pharmacodynamic and antitumor activity in solid tumor (HCT-116 colon and Calu-6 lung), lymphoma (OCI-Ly10, OCI-Ly19, and PHTX-22L), and AML (HL-60) xenograft models when subcutaneously (SC) administered to immunocompromised mice (Investigator's Brochure, 2018). Antitumor activity of MLN4924 (pevonedistat) in mice bearing HL-60 and THP-1 tumor xenografts was enhanced by combination treatment with azacitidine.

In *in vivo* safety studies in rats and dogs, gastrointestinal toxicity was most common (Investigator's Brochure, 2018). Most adverse events (AEs) resolved or reversed after a 2-week recovery period. Microscopic changes were observed in male and female reproductive organs in repeat-dose toxicology studies in both dogs and rats, therefore MLN4924 (pevonedistat) likely represents a substantial reproductive and developmental hazard. MLN4924 (pevonedistat) is primarily eliminated hepatically, and *in vitro*, MLN4924 (pevonedistat) is predominantly metabolized by the cytochrome P450 (CYP) isozyme 3A4. Thus, there is potential for drug-drug interactions if MLN4924 (pevonedistat) is co-administered with drugs that are CYP3A inhibitors or inducers. MLN4924 (pevonedistat) does not markedly inhibit or induce other CYP isozymes.

Detailed information regarding the nonclinical pharmacology and toxicology of MLN4924 (pevonedistat) is provided in the MLN4924 (pevonedistat) Investigator's Brochure (2018).

2.2.1.2 Clinical Experience with MLN4924 (pevonedistat)

The clinical development of MLN4924 (pevonedistat) started with four clinical trials with doses ranging from 25 to 278 mg/m^2 (Investigator's Brochure, 2018; Bhatia *et al.*, 2016; Sarantopoulos *et al.*, 2016; Shah *et al.*, 2016; Swords *et al.*, 2010). 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. The current understanding of the renal toxicity observed with MLN4924 (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.

Because of this, a revised risk mitigation strategy, including limiting the dose ≤100mg/m^2 for single-agent administration, was implemented across the MLN4924 (pevonedistat) program in October 2012. The revised risk mitigation strategy limited the dose to no higher than 50 mg/m2 for dosing on Days 1, 3, and 5 and no higher than 100 mg/m2 for dosing on Days 1, 4, 8, and 11 or 1, 8, and 15 for all studies for single-agent administration was implemented across the pevonedistat program. As of January 2019, approximately 436 additional patients have been treated with pevonedistat in single-agent and combination studies, and no Cycle 1 Day 1 SAEs as described above have been observed. These patients received pevonedistat at a dose of 50 to

100 mg/m2 as a single agent, a dose of 15 to 30 mg/m2 in combination with different standard of care (SOC) therapies, or a dose of 8 to 20 mg/m2 in combination with a CYP3A inhibitor. The Days 1, 3, and 5 schedule for pevonedistat infusion was chosen for further studies.

Accordingly, prophylactic use of dexamethasone was no longer used in all subsequent studies and no acute phase reactions have been observed in subsequent phase 1, phase 2 or phase 3 clinical trials. A phase 1 open label dose-escalation study including 53 patients with treatment-naïve AML assessed the MTD of MLN4924 (pevonedistat) on Days 1, 3, and 5 in combination with 75 mg/m^2 azacitidine (administered on a 5-on/2-off [weekend]/2-on schedule) in a 28-day treatment cycle in elderly patients with AML (Swords *et al*., 2015). The maximum tolerated dose (MTD) was determined to be 59 to 83 mg/m2. For patients with advanced solid tumors, a phase 1 open label, dose-escalation study was designed. A schedule of infusion on days 1-5 for MLN4924 (pevonedistat) was selected. The MTD for that schedule for patients with advanced solid tumors was determined to be 50 to 67 mg/m2 (Sarantopoulos *et al.*, 2016).

In a phase 1b study (C15009), MLN4924 (pevonedistat) plus docetaxel, gemcitabine, or the combination of carboplatin and paclitaxel was evaluated in three separate cohorts in solid tumors to determine the MTD and assess the safety, tolerability, and pharmacokinetics of MLN4924 (pevonedistat). Patients received MLN4924 (pevonedistat) with docetaxel (arm 1, n = 22), carboplatin plus paclitaxel (arm 2, n = 26), or gemcitabine (arm 3, n = 10) in 21-days (arms 1 and 2) or 28-days (arm 3) cycles. MLN4924 (pevonedistat) dose escalation was performed using an adaptive Bayesian continual reassessment method (CRM) on cycle 1 DLTs. The MTD for MLN4924 (pevonedistat) was determined to be 25 mg/m^2 with docetaxel and 20 mg/m^2 with carboplatin plus paclitaxel. The combination of MLN4924 (pevonedistat) plus gemcitabine was deemed intolerable due to myelosuppression and toxicity leading to delays and this cohort was closed to enrollment. The most frequently reported DLTs across all arms included grade 3 febrile neutropenia and increased ALT/AST; AST/ALT elevations were reversible with dose modifications. In general, the adverse events (AEs) of MLN4924 (pevonedistat) plus docetaxel or carboplatin plus paclitaxel were manageable. The most common AEs included fatigue, nausea, anemia, constipation, and diarrhea.

The combination of MLN4924 (pevonedistat)with carboplatin plus paclitaxel showed the most promising antitumor activity in pretreated patients (≥1 prior therapies). Notably, all but one of the eight responders in arm 2 and one responder in arm 2a had previously received platinum, taxanes, or both. The ORR in arm 2 was 35%, including two patients with CR (bladder cancer and endometrial carcinoma) (Lockhart *et al*., 2018)

These clinical studies overall demonstrated that MLN4924 (pevonedistat) was well-tolerated and the observed clinical benefit to patients treated with MLN4924 (pevonedistat) in combination with platinum-based chemotherapeutics supported further investigation with phase 2 trials. As of 22 January 2018, approximately 495 subjects (220 subjects for solid tumor indications) have received at least 1 dose of MLN4924 (pevonedistat) as part of MLN4924 (pevonedistat) clinical trials (Investigator's Brochure, 2018).

Table 1: Summary of ongoing or recently completed studies involving MLN4924 (pevonedistat) treatment:

NCT#/Phase	Status	Type of Cancer	Treatment	Assessment
NCT02122770 / Phase 1 Investigator's Brochure, (2018)	Completed	Solid tumors	MLN4924 (pevonedistat) (including CYP3A inhibitors); MLN4924 (pevonedistat) plus docetaxel or combination of carboplatin and paclitaxel	DDI
NCT02782468 / Phase 1	Active, not recruiting	AML/MDS	MLN4924 (pevonedistat); MLN4924 (pevonedistat) plus azacitidine	Safety, tolerability
NCT02610777 / Phase 2	Active, not recruiting	HR MDS, CMML, or low-blast AML	MLN4924 (pevonedistat) plus azacitidine; azacitidine	Efficacy, safety
NCT03057366 / Phase 1	Completed	Advanced solid tumor	MLN4924 (pevonedistat)	Mass balance
NCT03330106 / Phase 1	Recruiting	Advanced solid tumor	MLN4924 (pevonedistat); MLN4924 (pevonedistat) plus docetaxel or combination of carboplatin and paclitaxel	Corrected QT interval
NCT03459859 / Phase 1	Recruiting	AML/MDS	MLN4924 (pevonedistat) plus cytarabine	RPD2
NCT03486314 / Phase 1	Recruiting	Advanced solid tumors	MLN4924 (pevonedistat) plus rifampin; MLN4924 (pevonedistat) plus docetaxel or combination of carboplatin and paclitaxel	DDI

NCT03323034 / Phase 1	Recruiting	Recurrent or refractory solid tumors or lymphoma	MLN4924 (pevonedistat) plus temozolomide and irinotecan	MTD, RPD2, toxicity, and PK in pediatric population
NCT03386214 / Phase 1	Recruiting	Myelofibrosis	MLN4924 (pevonedistat) plus ruxolitinib	Safety, tolerability, MTD, frequency of AEs
NCT03268954 / Phase 3	Recruiting	HR MDS, CMML, or AML	MLN4924 (pevonedistat) plus azacitidine; azacitidine	EFS
NCT03009240 / Phase 1	Recruiting	HR AML	MLN4924 (pevonedistat) plus decitabine	DLTs, AEs, MTD
NCT03745352 / Phase 2	Planned (not yet recruiting)	Relapsed or refractory AML	MLN4924 (pevonedistat) plus azacitidine; azacitidine	OS
AE = adverse events, AML = acute myeloid leukemia, CMML = chronic myelomonocytic leukemia, DDI = drug-drug interaction, DLT = dose limiting toxicity, EFS = event free survival HR = high risk, MDS = myelodysplastic syndrome, MTD = maximum tolerated dose, OS = overall survival, PK = pharmacokinetics, RPD2 = recommended phase 2 dose				

2.3 Other Agents

2.3.1 Carboplatin

Carboplatin (NSC 241240) is one of the most widely utilized chemotherapeutic agents used in oncology. Carboplatin works primarily by forming DNA crosslinks that interrupt cellular DNA function and subsequently induce apoptosis, but also forms DNA adducts with other cellular components such as proteins, lipids, RNA, and mitochondrial RNA (Reed *et al*., 1996; Hermann *et al.,*2013). For more detailed information, please consult the carboplatin package insert (2011).

2.3.2 Paclitaxel

Paclitaxel (NSC 125973) is an anti-neoplastic agent that works by interfering with mitotic spindle function, resulting in disrupted chromosome segregation, inhibition of mitotic progression, prevention of cell division, and eventually cell death (Ganguly *et al.,* 2010). In hepatocytes, paclitaxel is metabolized by CYP2C8 to produce the major metabolite 6α-hydroxy-paclitaxel and is metabolized by CYP3A4 into 3-p-hydroxy-paclitaxel (Monsarrat *et al.*, 1998). For more detailed information, please consult the Taxol® package insert (2011).

2.4 Rationale

Platinum-based combination therapy is superior to best supportive care for patients with advanced, incurable NSCLC. Carboplatin is a platinum analog chemotherapeutic agent that has been in use since the 1980s. Platinum-based therapies function as alkylating agents by binding to cellular DNA to form inter-strand cross-linkages (ICLs). The DNA repair pathways that resolve DNA ICLs, such as nucleotide excision repair and homologous recombination, are coordinated by a DNA damage response pathway termed the Fanconi anemia pathway (Kee *et al.*, 2012). The key regulatory event in the Fanconi anemia pathway is monoubiquination of Fanconi anemia group D2 protein (FANCD2), which is required for multiple steps during ICL repair, including activation of the nucleotide excision repair and translesion synthesis, and recruitment of homologous recombination repair factors such as breast cancer 1/2 (BRCA1/2) and RecA-like recombinase 51 (RAD51) (Kee and D'Andrea, 2010). Preclinical data has demonstrated NEDD8 conjugation is necessary for the upstream phosphorylation of CHK1 and subsequent monoubiquitination of FANCD2 (Kee *et al.*, 2012). MLN4924 (pevonedistat) inhibits DNA damage-induced activation of the Fanconi anemia pathway and may sensitize cancer cells to DNA damaging agents such as platinum-based therapies.

Preclinical models demonstrate that MLN4924 (pevonedistat) chemosensitizes NSCLC cell lines to platinum chemotherapy (Kee *et al.*, 2012; Li *et al*., 2014; Bouck *et al*., 2015). In a primary xenograft squamous cell lung cancer model, the combination of MLN4924 (pevonedistat) and carboplatin led to greater tumor suppression compared to carboplatin or MLN4924 (pevonedistat) alone, or vehicle.

A phase 1b, multi-arm study (C15010) has studied the safety of carboplatin and paclitaxel in combination with MLN4924 (pevonedistat) in patients with solid tumors (Lockhart *et al*., 2018). Dose-limiting toxicities (DLTs) included Grade 3(G3) febrile neutropenia (n = 1; 15 mg/m^2), G3 aspartate transaminase (AST)/alanine transaminase (ALT) elevation (n = 2; 20 mg/m^2, n = 2; 25 mg/m^2). One DLT of G3 AST elevation occurred during MTD expansion. The recommended phase 2 dose (RP2D) was determined to be MLN4924 (pevonedistat) 20 mg/m^2 on Days 1, 3, and 5 in combination with carboplatin AUC = 5 and paclitaxel 175 mg/m^2 on the first day of a 21-day cycle. Overall, the combination was well tolerated with manageable toxicities. Common AEs included fatigue (56%), nausea (48%), anemia (41%), diarrhea (34%), and transaminitis (19%).

The combination of MLN4924 (pevonedistat) with carboplatin plus paclitaxel showed the most promising antitumor activity in pretreated patients (≥1 prior therapies) (Lockhart *et al*., 2015; Bauer *et al*., 2016; Lockhart *et al*., 2018). Notably, all but one of the eight responders in arm 2 and one responder in arm 2a had previously received platinum, taxanes, or both. The ORR in arm 2 was 35%, including two patients with CR (bladder cancer and endometrial carcinoma).

Consistent with preclinical studies reporting synergy between MLN4924 (pevonedistat) and platinum-chemotherapy, the objective responses in patients resistant to prior platinum/taxane therapy suggest the potential reversal of resistance by the addition of MLN4924 (pevonedistat).

Carboplatin in combination with paclitaxel has been proven effective in NSCLC and is

commonly used as backbone chemotherapy regimen for patients with NSCLC (Sandler *et al*., 2006). The median PFS for this regimen is 4.5 months. Adding MLN4924 (pevonedistat) is an attractive strategy to further enhance the activity of this regimen and overcome platinum resistance; especially in the re-treatment setting. In addition, identifying patients who are most likely to benefit from this strategy will be explored by qualitative assessment of NAE1 and UBC12 protein expression on tumor using immunohistochemistry (IHC). The hypothesis is that patients with high tumor NAE1 and UBC12 expression, which could help identify patients who have overexpression of the neddylation pathway, will benefit from the addition of NAE1 inhibition with MLN4924 (pevonedistat).

Given these safety data, objective responses in patients resistant to prior platinum/taxane therapy, and rationale, we propose a phase 2, single arm study of MLN4924 (pevonedistat) 20 mg/m^2 (Days 1, 3, 5) in combination with carboplatin AUC = 5 (Day 1) and paclitaxel 175 mg/m^2 (Day 1) in patients with advanced NSCLC previously treated with immunotherapy and platinum chemotherapy, including patients initially treated with front-line combination of platinum-based chemotherapy and immunotherapy (PD-1 inhibitor such as pembrolizumab).

2.5 Correlative Studies Background

2.5.1 Integrated Studies

2.5.1.1 NQO1 and SLC7A11 Gene Expression

This 12-gene assay will be used to test pharmacodynamic markers for drug response based on MLN4924 (pevonedistat) mechanism of action, previously characterized by Takeda. Increased level of NRF2 is a biomarker of MLN4924 (pevonedistat) activity. Samples will be obtained on Cycle 1 Day 1, pre-treatment and 6 hours (+/- 5 min) post-infusion on all patients enrolled in this study.

2.5.1.2 CTCs

CTCs can be found in the blood of patients with advanced NSCLC and can serve as a minimally invasive liquid biopsy for longitudinal evaluation of markers of treatment response and resistance. CTCs are isolated and quantified using Exclusion-based Sample Processing (ESP) technology (Salus Discovery, Madison, WI). We will evaluate changes in the total number of CTCs and the percentage of CTCs positive for γH2AX and RAD51 foci. CTCs will be obtained on all patients at baseline, Cycle 3 Day 1, and upon progression with MLN4942 (pevonedistat) to evaluate the correlation between markers of DNA damage and response to the MLN4924 (pevonedistat) based on imaging.

2.5.1.3 Pharmacokinetic parameters (PKs)

In the phase 1b study of MLN4924 (pevonedistat) in combination with carboplatin and paclitaxel, there was a trend toward higher MLN4924 (pevonedistat) plasma concentrations when given with carboplatin plus paclitaxel, compared with a single-agent administration. Although some overlap exists in the metabolizing enzymes and/or transporter proteins involved

in the drug clearance of MLN4924 (pevonedistat) and carboplatin and paclitaxel, none are known inhibitors or inducers. This warrants further investigation. PKs will be done on Cycle 1 Day 1.

2.5.2 Exploratory Studies

2.5.2.1 NAE inhibition-responsive genes: *ATF3, B2M, GCLM, GSR, MAG1, RPLPO, TXNRD1*, and *UBC* Gene Expression

To determine the expression of pharmacodynamic markers induced by NAE inhibition: *ATF3, B2M*, *GCLM*, *GSR*, *MAG1*, *RPLP0*, *SRXN1*, *TXNRD1*, and *UBC*. This will be performed pre-treatment and 6 hours (+/- 5 min) post-treatment on Cycle 1 Day 1.

2.5.2.2 Tumor NAE1 and UBC12 Protein Expression

Previous studies demonstrated that higher expression of NAE1 and UBC12 was associated with poor overall survival in lung cancer. The hypothesis is that patients with higher tumor NAE1 and UBC12 expression will benefit from NAE inhibition with MLN4924 (pevonedistat). Identifying patients who are most likely to benefit from this strategy will be explored by qualitative assessment of NAE1 and UBC12 protein expression on tumors using IHC and correlating this with clinical outcomes (ORR, PFS, OS). Baseline archival tumor samples will be optional but encouraged from patients when tissue is available. We anticipate obtaining at least 20 samples.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must be ≥18 years old. Because no dosing or AE data are currently available on the use of MLN4924 (pevonedistat) in combination with carboplatin and paclitaxel in patients <18 years of age, children are excluded from this study, but may be eligible for future pediatric trials.

3.1.2 Patients must have histologically confirmed stage IIIB or IV NSCLC (squamous or nonsquamous) that is metastatic or unresectable.

3.1.3 Patients must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1.

3.1.4 Patients must have progressed on prior treatment with checkpoint inhibitor (PD-1/PD-L1 inhibitors) either as a single-agent therapy or in combination, as below. Patients will be eligible if there is a contra-indication to checkpoint inhibitor therapy.

a. Patients who have progressed after receiving a checkpoint inhibitor in combination with a platinum-based doublet, as first-line treatment for NSCLC.
b. Patients who have progressed on checkpoint inhibitor as second-line therapy, after receiving a platinum-based doublet as first-line therapy.
c. Patients who have progressed on platinum-based doublet as second-line therapy, after receiving a checkpoint inhibitor as first-line therapy.

3.1.5 Patients must have disease progression on or after platinum-based chemotherapy for metastatic disease or within 6 months of completion of platinum-based chemotherapy administration as adjuvant/neoadjuvant chemotherapy or concurrent chemoradiation.

3.1.6 Patients must have adequate organ function:

- Absolute neutrophil count ≥1,500/mcL
- Platelet count ≥150,000/mcL
- Total bilirubin ≤1 x institutional upper limit of normal (ULN)
  - Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5 x ULN
- AST(SGOT)/ALT(SGPT) ≤3.0 × institutional ULN,
  - Patients with metastatic liver disease may enroll if ≤5xULN
- glomerular filtration rate (GFR) >30 mL/min/1.73 m^2

3.1.7 Known HIV positive patients who meet the following criteria will be considered eligible:

- CD4 count >350 cells/mm^3
- Undetectable viral load within the last six months
- HIV positive patients must be stable on HAART. Clinically significant metabolic

enzyme inducers are not permitted during this study(e.g., ritonavir, efavirenz, nevirapine).
- No history of Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infections

3.1.8 Eastern Cooperative Oncology Group (ECOG) performance status 0-1 (See Appendix A).

3.1.9 Life expectancy ≥ 12 weeks.

3.1.10 Patients are eligible if CNS metastases are adequately treated and neurological symptoms have returned to baseline or are controlled for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on stable or decreasing dose of steroids. Patients with leptomeningeal disease are excluded.

3.1.11 The effects of MLN4924 (pevonedistat) on the developing human fetus are unknown. For this reason and because agents as well as other therapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study or within 4 months of completion, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of MLN4924 (pevonedistat) administration.

Female patients who:
- Are postmenopausal for at least 1 year before the screening visit, or
- Are surgically sterile, or

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

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

contraception.)

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

3.1.13 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.

3.1.14 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.

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

3.1.16 Ability to understand and the willingness to sign a written informed consent document. Participants 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.

3.1.17 Patients with NSCLC harboring genomic aberrations (e.g. sensitizing EGFR, ALK, ROS1, NTRK, BRAF V600E mutation positive) must have received prior treatment with FDA approved targeted therapy for patients for which FDA approved targeted therapies is available.

3.2 Exclusion Criteria

3.2.1 Patients who have not recovered from AEs due to prior anti-cancer therapy (*i.e.*, have residual toxicities > Grade 1) with the exception of alopecia and neuropathy.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MLN4924 (pevonedistat), carboplatin, or paclitaxel.

3.2.4 Patients who have had chemotherapy or radiotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study.

3.2.5 Patients with uncontrolled intercurrent illness.

3.2.6 Patients with psychiatric illness/social situations that would limit compliance with study requirements.

3.2.7 Pregnant women are excluded from this study because MLN4924 (pevonedistat), carboplatin, and paclitaxel have the potential for teratogenic or abortifacient effects.

Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with MLN4924 (pevonedistat), breastfeeding must be discontinued if the mother is treated with MLN4924 (pevonedistat). These potential risks may also apply to other agents used in this study.

3.2.8 Female patients who intend to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s).

3.2.9 Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s).

3.2.10 Known cardiopulmonary disease defined as:

- Unstable angina
- Congestive heart failure (New York Heart Association [NYHA] Class III or IV;);
- Myocardial infarction within 6 months prior to first dose (patients who had ischemic heart disease such as acute coronary syndrome [ACS], myocardial infarction, and/or revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll)
- Symptomatic cardiomyopathy
- Clinically significant arrhythmia:
    1. History of polymorphic ventricular fibrillation or torsade de pointes,
    2. Permanent atrial fibrillation, 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 screening,
    4. Grade 3 atrial fibrillation defined as symptomatic and incompletely controlled medically, or controlled with device (*e.g.*, pacemaker), or ablation in the past 6 months and
    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.
- Clinically symptomatic pulmonary hypertension requiring pharmacologic therapy

3.2.11 Peripheral neuropathy that is Grade ≥3, or Grade 2 with pain on clinical examination during the screening period.

3.2.12 Uncontrolled high blood pressure (*i.e.,* systolic blood pressure >180 mmHg, diastolic blood pressure >95 mmHg).

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

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

3.2.15 Major surgery within 14 days before the first dose of any study drug or a scheduled

surgery during study period.

3.2.16 Life-threatening illness unrelated to cancer.

3.2.17 Patients with uncontrolled coagulopathy or bleeding disorder.

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

3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

4. REGISTRATION PROCEDURES

4.1 Investigator and Research Associate Registration with CTEP

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 Oncology Patient Enrollment Network (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, and
- Assign the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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.

4.2 Site Registration

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

IRB Approval

Sites participating with the NCI Central Institutional Review Board (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 PI (*i.e.*, the investigator on the IRB/REB approval) must meet the following five 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 Federalwide Assurance (FWA) number,
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization, and
- Compliance with all protocol-specific requirements (PSRs).

4.2.1 Downloading Regulatory Documents

Download the site registration forms from the protocol-specific 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 Participating Organization on the protocol.

- Log on to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password,
- Click on *Protocols* in the upper left of your screen
  - Enter the protocol number in the search field at the top of the protocol tree, or
  - Click on the By Lead Organization folder to expand, then select LAO-MD017, and protocol number 10266,
- Click on *Documents*, select *Site Registration*, 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.)

4.2.2 Requirements for NCI Protocol #10266 Site Registration

- Site Initiation Visit. Contact the Principal Investigator and Protocol Contact to schedule the SIV. Documentation of the SIV will be submitted to the CTSU by the Protocol Contact.
- Specimen Tracking System Training Requirement:
  - All data entry users (Clinical Research Associate role) at each participating site will need to complete the Theradex-led training.
  - Theradex will provide a certificate of completion, which will need to be submitted to the CTSU through the Regulatory Submission Portal.
  - The training is a one-time only requirement per individual. If an individual has previously completed the training for another ETCTN study, the training does not need to be completed again nor does the certificate of completion need to be resubmitted to the CTSU. However, new versions of the Specimen Tracking System may require new training.
  - This training will need to be completed before the first patient enrollment at a given site.
  - Peter Clark and Diana Vulih are the main points of contact at Theradex for the training (PClark@theradex.com and DVulih@theradex.com, Theradex phone: 609-799-7580).

4.2.3 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 →

Regulatory → Regulatory Submission.

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

4.2.4 Checking **Site** Registration Status

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

- Log on to the CTSU members' website
- Click on *Regulatory* at the top of your screen
- Click on *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.

4.3 Patient Registration

4.3.1 OPEN / IWRS

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 an LPO roster, ETCTN Corresponding roster, or Participating Organization roster with the role of Registrar. Registrars must hold a minimum of an AP registration type.
- If a DTL is required for the study, the registrar(s) must hold the OPEN Registrar task on the DTL for the site.
- 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. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes, and
- 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 members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

4.3.2 Special Instructions for Patient Enrollment:

This Study will use the ETCTN Specimen Tracking System (STS).

- All biospecimens collected for this trial must be submitted using the ETCTN Specimen Tracking System (STS) unless otherwise noted.
- The system is accessed through special Rave user roles: "CRA Specimen Tracking" for data entry at the treating institutions and "Biorepository" for users receiving the specimens for processing and storage at reference labs and the Biorepository.
- Please refer to the Medidata Account Activation and Study Invitation Acceptance link on the CTSU website under the Rave/DQP tab.
- **Important: Failure to complete required fields in STS may result in a delay in sample processing.** Any case reimbursements associated with sample submissions will not be credited if samples requiring STS submission are not logged into STS.

Detailed instructions can be found in Section 5.3

4.3.3 OPEN/IWRS Questions?

Further instructional information on OPEN is provided on the OPEN tab 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.

4.4 General Guidelines

Following registration, patients should begin protocol treatment within 7 business days. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Protocol Contact should be notified of cancellations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 Summary Table for Specimen Collection

Biomarker Name	Collection Time Point	Specimen and Quantity	Send Specimens to:
Baseline			
NAE1, UBC12 protein expression	Pre-study	• Formalin-Fixed Paraffin Embedded (FFPE) tumor tissue (archival tissue), 6 slides per patient[a,b]	University of Wisconsin
Cycle 1, Day 1			
NAE inhibition-responsive genes, *NQO1, SLC7A11*	Pre-treatment; 6hr +/- 5 min post-infusion	• Blood (PAXgene Blood RNA tube, 2.5mL)	Asuragen
PK analysis	Pre-infusion, immediately post infusion, 3 hours (+/- 5 min), 12 hours (+/- 2 hours) (optional), 24 hours (+/- 2 hours), and 48 hours (+/- 2 hours) post-infusion	• 3.0mL blood in K_2EDTA lavender top Becton-Dickinson Vacutainer o Submit 1 cryovial containing plasma for each time point o Store the 2nd cryovial containing plasma for each time point on-site at -70ºC or lower as backup	QPS
CTCs	Pre-treatment	• Blood (2x EDTA tubes, 10mL and 2x CellSave tubes, 10mL)	University of Wisconsin
Cycle 3, Day 1			
CTCs	Pre-treatment	• Blood (2x EDTA tubes, 10mL and 2x CellSave tubes, 10mL)	University of Wisconsin
Progression			
CTCs		• Blood (2x EDTA tubes, 10mL and 2x CellSave tubes, 10mL)	University of Wisconsin

AT=archived tumor, PK=pharmacokinetics, CTCs=circulating tumor cells
a: If 6 slides are not available, 4 slides will be sufficient
b: Optional study

5.2 Specimen Procurement Kits and Scheduling

5.2.1 Specimen Collection and Shipping Kits

Institutional supplies must be used for specimen collection and processing.

5.2.1.1 Scheduling of Specimen Collections

Please adhere to the following guidelines when scheduling procedures to collect tissue:

- Tumor tissue specimens collected during biopsy procedures and fixed in formalin must be shipped on the same day of collection.
- Tissue can be collected Monday through Wednesday and shipped overnight for arrival on Tuesday through Thursday at the University of Wisconsin.

Specimens submitted frozen such as frozen plasma can be collected on any day but must be stored frozen and shipped to QPS on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained at -70°C or lower.

Fresh blood specimens for CTC analysis may be collected and shipped Monday through Thursday to the UWCCC Circulating Biomarker Core.

Specimens submitted frozen such as frozen blood can be collected on any day but must be stored frozen and shipped to Asuragen on Monday through Thursday. In the event that frozen specimens cannot be shipped immediately, they must be maintained at -70°C.

5.3 Specimen Tracking System Instructions

5.3.1 Specimen Tracking System Overview and Enrollment Instructions

For the ETCTN STS, the following information will be requested:

- Protocol Number
- Investigator Identification
  - Institution and affiliate name
  - Investigator's name
- Eligibility Verification: Patients must meet all the eligibility requirements listed in Section 0.
- Additional Requirements: Patients must provide a signed and dated, written informed consent form.

Upon enrolling a patient, IWRS will communicate with OPEN, assigning two separate and unique identification numbers to the patient, a Universal patient ID (UPID) and a Treatment patient ID. The UPID is associated with the patient and used each and every time the patient engages with the portion of this protocol that uses the ETCTN Specimen Tracking System. The UPID contains no information or link to the treatment protocol. IWRS will maintain an association between the UPID for ETCTN biobanking and molecular characterization and any treatment protocols the patient participates in, thereby allowing analysis of the molecular characterization results with the clinical data.

Immediately following enrollment, the institutional anatomical pathology report for the diagnosis under which the patient is being enrolled must be uploaded into Rave. The report must include the surgical pathology ID (SPID), collection date, block number, and the IWRS-assigned UPID and patient study ID for this trial. For newly acquired biopsies, the radiology and operative report(s) must also be uploaded into Rave. **Important: Remove any personally identifying information, including, but not limited to, the patient's name, initials, medical record number, and patient contact information from the institutional pathology report prior to**

submission.

Additionally, please note that the STS software creates pop-up windows when reports are generated, so you will need to enable pop-ups within your web browser while using the software.

For questions regarding the Specimen Tracking System, please contact the Theradex Help Desk at CTMSSupport@theradex.com.

A shipping manifest **must** be included with all sample submissions.

5.3.2 Specimen Labeling

5.3.2.1 Blood Specimen Labels for CTCs

Include the following on blood specimens (including whole blood and frozen, processed blood products – like serum and plasma):

- Protocol number concatenated to the Subject Study ID
- Universal Subject ID (UPID)
- Rave generated specimen ID (which includes the protocol number and Universal Subject ID along with a sequential integer representing the order the specimen was collected
- Protocol timepoint
- Specimen type (*e.g.,*. blood, serum)
- Collection date and time

5.3.2.2 Blood Specimen Lables for PK analysis

- Protocol Number
- Subject Identification Number
- Sample Identification Code shown below. [nominal time] may be the scheduled vist and/or time point.
    a) Plasma PK Pevo [nominal time] Set1
    b) Plasma PK Pevo [nominal time] Set 2

5.3.2.3 Blood Specimen Labels for NAE inhibition-responsive genes and *NQO1, SLC7A11*

Label each specimen with the following information:

- Protocol #:
- Study ID #
- Specimen type: Pharmacodynamics
- Specimen time point: pre or post
- Date/time collected

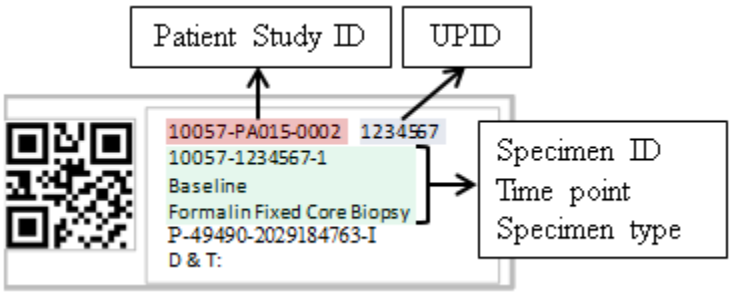
5.3.2.4 Tissue Specimen Labels

Include the following on all tissue specimens or containers (*e.g.*, formalin jar):

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, FFPE Block, Formalin Fixed Tissue, Fresh Tissue in Media, *etc.*)
- Tissue type (P for primary, M for metastatic or N for normal)
- Surgical pathology ID (SPID) number
- Block number from the corresponding pathology report (archival only)
- Collection date (to be added by hand)

5.3.2.5 Example of Specimen Label

The following image is an example of a tissue specimen label printed on a standard Avery label that is 1" high and 2.625" wide.



The QR code in the above example is for the Specimen ID shown on the second line.
NOTE: The QR code label is currently under development at Theradex as of 31-Aug-2018; therefore, labels generated by the STS for this study may not include a QR code.

The second line item from the end includes four data points joined together:

1. Tissue only: Primary (P), Metastatic (M), Normal (N) tissue indicated at the beginning of the specimen ID; this field is blank if not relevant (*e.g.*, for blood)
2. Block ID or blank if not relevant
3. SPID (Surgical Pathology ID) or blank if none
4. The last alpha-numeric code is protocol specific and is only included if the protocol requires an additional special code classification

The last line on the example label is for the handwritten date and optional time.

5.3.3 Overview of Process at Treating Site

5.3.3.1 OPEN Registration

All registrations will be performed using the OPEN system. OPEN communicates automatically with the IWRS which handles identifier assignments, any study randomization, and any

prescribed slot assignments. If specimen analysis is required to determine eligibility, the protocol will be setup with multi-step registration.

Registration without eligibility specimen analysis

1. Site enters registration data into OPEN during one or more steps.
2. IWRS receives data from OPEN, generates the Subject Study ID and the UPID, both of which are sent back to OPEN.
3. IWRS sends all applicable registration data directly to Rave at the end of the final registration step.

Any data entry errors made during enrollment should be corrected in Rave.

5.3.3.2 Rave Specimen Tracking Process Steps

Step 1: Complete the **Histology and Disease** form (but do not upload reports until a specimen label can be applied to them) and the Baseline forms regarding **Prior Therapies**. Enter the initial clinical specimen data:

- **Specimen Tracking Enrollment** CRF: Enter Time Point, Specimen Category, Specimen Type, Block number, Tissue type, Surgical Path ID, and number of labels needed (include extra labels to apply to reports to be uploaded). CRF generates unique Specimen ID.

Step 2: Print labels using report in EDC and collect specimen.

- Label specimen containers and write collection date *[if the study also requires recording the collection time on the label, include the time]* on each label.
- After collection, store labeled specimens as described in Section 5.4.2.
- Apply an extra specimen label to *each* report before scanning. Return to the **Histology and Disease** form to upload any initial Pathology, Radiology, Molecular Reports (up to 4), Surgical (or Operative) reports and Pathology Verification form (when applicable). Return to **Specimen Tracking Enrollment** CRF to upload any molecular report (one per specimen) and/or specimen specific pathology or related report (one per specimen). Uploaded reports should have protected health information (PHI) data, like name, mailing address, medical record number or social security number (SSN), redacted. Do not redact SPID, block number or relevant dates, and include the UPID and patient study ID on each document.

Step 3: Complete specimen data entry.

- **Specimen Transmittal** Form: Enter collection date and time and other required specimen details.

Step 4: When ready to ship, enter shipment information.

- **Shipping Status** CRF: Enter tracking number, your contact information, recipient, number of containers and ship date once for the first specimen in a shipment.
- **Copy Shipping** CRF: Select additional specimens to add to an existing shipment referenced by the tracking number.

Step 5: Print shipping list report and prepare to ship.

- Print two copies of the shipping list, one to provide in the box, the other for your own records.
- Print pathology or other required reports to include in the box. Be sure the printed copy includes the specimen label.

Step 6: Send email notification.

- For only one of the specimens in the shipment, click "Send Email Alert" checkbox on the **Shipping Status** CRF to email recipient.

Step 7: Ship the specimen(s)

5.4 Specimen Collection

5.4.1 Archival FFPE Tumor Specimen

If previously-collected FFPE tissue will be submitted, then the following criteria must be met:

- Tissue collected within 6 months prior to registration is preferred. If tissue collected within 6 months not available, any archival tissue specimen will be acceptable.

The following samples are requested, if available:

- FFPE block samples will be shipped to the Wheeler lab, then will be submitted to the Translational Research Initiatives in Pathology (TRIP) lab for sectioning.
- Six unstained slides, 4 μm on positive charged slides for immunohistochemistry analysis. If 6 slides are not available, 4 unstained slides will be sufficient.

5.4.2 Blood Collection

5.4.2.1 Collection of Blood in PAXgene tube

1. Blood samples will be collected pre-treatment and 6 hr (+/- 5 min) post-treatment. Collect one 2.5 mL of blood in PAXgene tube at each time point.
2. Ensure that the PAXgene tube is at room temperature (18°C–25°C) prior to use and properly labeled with patient identification.
3. Using a blood collection set, collect blood into the PAXgene Blood RNA tube using your institution's recommended standard procedure for venipuncture.
4. Hold the PAXgene blood RNA tube vertically, below the donor's arm during blood collection.
5. Allow at least 10 seconds for a complete blood draw to take place. Ensure that the blood has stopped flowing into the tube before removing the tube from the holder.
6. Gently invert PAXgene Blood RNA Tube 8 to 10 times.
7. "Slow-freeze" tube overnight at -20°C. The tube may then be shipped or transferred to a -70°C freezer for long-term storage until shipped.

5.4.2.2 Collection of Blood in EDTA and CellSave Tubes

1. Label tubes according to the instructions in Section 5.3.1.1.
2. Collect blood into 2, 10 ml EDTA tubes and gently invert tube 8 – 10 times to mix.
3. Collect blood into 2, 10 ml Cellsave tubes and gently invert tube 8 – 10 times to mix.
4. Ship on day of collection for next day delivery according to instructions below.

5.4.2.3 Collection of Blood in K2EDTA lavender top Beckton Dickinson Vacutainers

1. Legibly write the subject's initials and subject identification number clearly using blue or black pen only (no markers) on blood collection tubes. Cryovial labels must be labeled according to section 5.3.2.2.
2. Collect 3.0 mL of venous blood into a chilled K_2EDTA lavender top Becton-Dickinson Vacutainer.
3. Gently invert the Vacutainer 8 to 10 times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
4. Centrifuge the Vacutainers for 10 minutes at approximately 1100-1300 × g (RDF) at approximately 4 °C in a refrigerated centrifuge. Note: if using a collection device other than Becton-Dickinson, refer to manufacturer's instruction for proper centrifugation force and time.
5. Immediately following centrifugation, gently remove plasma from the packed cells and transfer into two appropriately labeled 2.0 mL cryogenic vials. To ensure a more homogenous sample, transfer all plasma into one cryovial. From there, split the plasma evenly between the 2 aliquots. A minimum of 0.6 mL needs to be obtained for each aliquot.
6. Cap the labeled storage tubes and freeze the plasma samples immediately at approximately -70 °C or lower. If a -70 °C freezer is not available, freeze and store samples at-20 °C. No more than 45 minutes will elapse between blood collection and freezing the plasma sample.
7. Store samples frozen at approximately -70 °C or lower until shipment.

5.5 Shipping Specimens from Clinical Site to Analysis Laboratories

5.5.1 Shipping Fresh Blood (EDTA and CellSave Tubes)

1. Before packaging specimens, verify that each specimen is labeled according to Section 5.3.1.
2. Each shipment should include a Sample Inventory.
3. Notify the Circulating Biomarker Core of the shipment with sample inventory copy via email (uwctc@medicine.wisc.edu) ahead of time, or at the latest on the day of shipment, please include tracking information in email.
4. Samples will be packed in Styrofoam shipping containers containing two ambient gel packs surrounding blood tubes. Samples should never be frozen.

5.5.1.1 Shipping to the University of Wisconsin Carbone Cancer Center (UWCCC) Circulating Biomarker Core

Name: Dr. Joshua Lang
Attn: Dr. Jennifer Schehr
University of Wisconsin Carbone Cancer Center
Address:
Circulating Biomarker Core
K4/517 Clinical Science Center
University of Wisconsin Carbone Cancer Center
600 Highland Avenue
Madison, WI 53792
Lab phone: (608) 265-5349
Office phone: (608) 262-0705
Fax: (608) 265-0614
Email: uwctc@medicine.wisc.edu

5.5.2 Shipping of Archival tissue

1. Before packing specimens, verify that each specimen is labeled according to Section 5.3.3.
2. Each shipment should be included with a Sample Inventory.
3. Notify the Wheeler lab ahead of the shipment with sample copy via email (address below) ahead of time on the day of shipment. Shipments should be done Monday – Thursday only for lab to receive Tuesday – Friday.
4. Samples will be packed in biological shipment-appropriate box.
5. Samples should be ambient, not refrigerated.

5.5.2.1 Shipping to the Wheeler Laboratory

Attn: Mari Iida
Wisconsin Institute for Medical Research
WIMR 3100
Address: 1111 Highland Ave, Madison, WI 53705
Phone: (608) 265-5446
Email: dlwheeler@wisc.edu; Iida@humonc.wisc.edu

5.5.3 Shipping of Frozen Blood (in PAXgene tubes)

1. Ship the frozen samples Monday through Thursday on the day after collection or store at -70°C and ship on the next available day.

5.5.3.1 Shipping to Asuragen

Deepa Eveleigh, Associate Director, CLIA/Custom Dx Operations / Asuragen
Address: 2150 Woodward Street, Suite 100, Austin, TX 78744

Email: develeigh@asuragen.com
Job Reference Code: JB13048

5.5.4 Shipping of Frozen Blood (in K_2EDTA lavender top Beckton-Dickson Vacutainers)

1. All samples should be shipped to the address below.
2. Primary and backups of samples should not be shipped together. Ship the primary samples together (1 cryovial per time point) and store the backup samples (2nd cryovial per time point) at -70 or lower until requested.
3. Each shipment should include a sample inventory.
4. Please notify TBD of the shipment with the sample inventory copy via email ahead of time or at the last day of shipment.
5. Samples will be packed in Styrofoam shipping containers with sufficient amount of dry ice to maintain frozen conditions for at least 72 hours (3 days) or up to the expected delivery date, whichever is longer.

5.5.4.1 Shipping to QPS

Attn: Sample Coordination Team
QPS, LLC
3 Innovation Way
Suite 240
Newark, DE, 19711
Phone: +1 302 369 5120
Email: sample@qps.com

5.6 Biomarker Plan

List of Biomarker Assays in Order of Priority

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Specimen(s) and Time Points	Laboratory
1	*NQO1, SLC7A11*	RT-PCR	Integrated Pharmacodynamic marker induced by NAE inhibition	M	Whole blood Cycle 1: Day 1 (pre-treatment, 6 hours (+/- 5 min) post infusion)	Asuragen; Deepa Eveleigh (develeigh@asuragen.com)
2	Total CTC number, number of γH2AX+ CTC, number of RAD51+ CTCs	Versa	Integrated Identify potential prognostic and predictive biomarkers of MLN4924 (pevonedistat). To compare changes in the number of γH2AX and RAD51 positive CTCs at baseline, Cycle 3, Day 1 and progression with MLN4924 (pevonedistat).	M	Blood Cycle 1: Day 1, Cycle 3: Day 1 (with disease evaluation imaging) and at progression	UWCCC Circulating Biomarker Core; (uwctc@medicine.wisc.edu)
3	PK analysis	LC-MS/MS	Integrated Confirmatory assessment: prior combination trial showed potential interaction (increased MLN4924 (pevonedistat))	M	Blood Cycle 1: Day 1 (pre-infusion, immediately post infusion, and 3 hours (+/- 5 min), 12 hours (+/- 2 hours) (optional), 24 hours (+/- 2 hours), and 48 hours (+/- 2 hours post infusion)	QPS Lily Rosa Lily.rosa@qps.com

Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Specimen(s) and Time Points	Laboratory
4	NAE1, UBC12 protein expression	IHC	Exploratory Identify predictive biomarker: high expression of NAE1 and UBC12 proteins will correlate with improved outcome	O	Tumor tissue Baseline (performed on archival tissue)	University of Wisconsin; Deric L. Wheeler (dlwheeler@wisc.edu)
5	NAE inhibition-responsive genes: (*ATF3, B2M GCLM, GSR, MAG1, RPLPO, SRXN1, TXNRD1, UBC)*	RT-PCR	Exploratory Pharmacodynamic marker induced by NAE inhibition	O	Whole blood Cycle 1: Day 1 (pre-treatment, 6 hours (+/- 5 min) post infusion)	Asuragen; Deepa Eveleigh develeigh@asuragen.com

ATF3 = cyclic AMP-dependent transcription factor 3, *B2M* = β_2 microglobulin, CTC = circulating tumor cells, *GCLM* = glutamate-cysteine ligase regulatory subunit, *GSR* = glutathione-disulfide reductase, IHC = immunohistochemistry, LC-MS/MS = liquid chromatography/mass spectrometry, M = mandatory, *MAG1* = DNA-3-methyladenine, NAE1 = NEDD8-activating enzyme, *NQO1* = NAD(P)H: quinone oxidoreductase1, O = optional, PK = pharmacokinetics, *SLC7A11* = sodium independent cystine-glutamate antiporter, *RPLP0* = ribosomal protein lateral stalk subunit P0, RT-PCR = reverse transcription polymerase chain reaction, *SRXN1* = sulfiredoxin-1, *TXNRD1* = thioredoxin reductase 1, *UBC* = ubiquitin-conjugating enzyme.

5.7 Integrated Studies

5.7.1 *NQO1* and *SCL7A11* (NRF2 target genes)

This 12-gene assay will be used to test pharmacodynamics markers for drug response based on MLN4924 (pevonedistat) mechanism of action, previously characterized by Takeda. Increased level of NRF-2 is a biomarker of MLN4924 (pevonedistat) activity. Samples will be obtained on Cycle 1 Day 1, pre-treatment and 6 hours (+/- 5 min) post infusion on all patients enrolled in this study.

5.7.1.1 Specimen Receipt and Processing

1. The samples are stable for up to 3 days at room temperature, up to 5 days at 2-8 °C and up to 4 years at – 20 °C or -70 °C.
2. All samples to be shipped to address listed in Section 5.5.

5.7.1.2 Site Performing Correlative Study

NQO1 and *SCL7A11* RT-PCR will be performed in the Asuragen Lab under the direction of Deepa Eveleigh.

5.7.2 CTCs

CTCs will be obtained pretreatment, and at disease progression for all patients. CTCs will be obtained on all patients at baseline, Cycle 3 Day 1, and upon progression not evaluate for number of γH2AX and RAD51 CTCs.

5.7.2.1 Specimen receipt and processing

1. Ship samples on the same day of blood draw.
2. All samples to be shipped to address listed in Section 5.5.

5.7.2.2 Site Performing Correlative Study

CTC ESP assay will be performed at the UWCCC Circulating Biomarker Core

5.7.3 PK Analysis

Confirmatory assessment: prior combination trial showed potential interactions with MLN4924 (pevonedistat). This will be performed on Cycle 1 Day 1 pre-infusion, immediately post-infusion, and 3 hours ± 5 minutes, 12 hours ± 1 hour, 24 hours ± 2 hours, and 48 hours ± 2 hours post-infusion.

5.7.3.1 Specimen receipt and processing

1. Keep samples frozen at -70ºC or lower until shipment.
2. If a -70ºC freezer is not available, samples can be stored in a -20ºC freezer for up to 30

days.
3. All samples to be shipped to address listed in Section 5.5.

5.7.3.2 Site Performing Correlative Study

PK analysis will be performed at QPS.

5.8 Exploratory/Ancillary Studies

5.8.1 NAE inhibition-responsive genes: *ATF3, B2M, GCLM, GSR, MAG1, RPLPO, SRXN1, TXNRD1, and UBC*

To determine expression of pharmacodynamic markers induced by NAE inhibition: *ATF3, B2M, GCLM, GSR, MAG1, RPLP0, SRXN1, TXNRD1*, and *UBC*.

5.8.1.1 Specimen receipt and processing

- The samples are stable for up to 3 days at room temperature, up to 5 days at 2-8ºC, and up to 4 years at -20ºC or -70ºC.
- All samples to be shipped to address listed in Section 5.5.

5.8.1.2 Site Performing Correlative Study

ATF3, B2M, GCLM, GSR, MAG1, RPLPLO, SRXN1, TXNRD1, and *UBC* RT-PCR will be performed in the Asuragen Lab under the direction of Deepa Eveleigh.

5.8.2 NAE1 and UBC12 protein expression

Previous study demonstrated that higher expression of NAE1 and UBC12 was associated with poor overall survival in lung cancer. The hypothesis is that patients with high tumor NAE1 and UBC12 expression, which is negatively prognostic, will benefit from NAE inhibition with MLN4924 (pevonedistat). Identifying patients who are most likely to benefit from this strategy will be explored by qualitative assessment of NAE1 and UBC12 protein expression on tumor using IHC. Antibodies for NAE1 and UBC12 have been established for use on human FFPE tissue (Li *et al*., 2014). Baseline archival tumor samples will be optional and encouraged to be obtained from patients when tissue is available. We anticipate obtaining at least 20 samples. This will be correlated with clinical outcomes (PFS, ORR, OS)

5.8.2.1 Specimen receipt and processing

All samples to be shipped to address listed in Section 5.5.

5.8.2.2 Site Performing Correlative Study

NAE1 and UBC12 IHC will be performed at the University of Wisconsin laboratory of Dr. Deric Wheeler. Six 4 μm slides will be utilized for immunohistochemistry analysis in Wheeler lab (1

no antibody, 1 NAE antibody dilution 1, and 1 NAE antibody dilution 2 as well as no antibody, 1 UBC antibody dilution 1, and 1 UBC antibody dilution 2). If 6 slides are not available, 4 slides will be sufficient.

5.8.3 Banking and Use of Specimens in Future Research

Any biospecimens remaining after processing will be retained indefinitely at the University of Wisconsin biobank under appropriate storage conditions. Specimen types may include:

- Blood
- Archival tissue

Specimens from patients who consented to allow their specimens to be used for future approved research studies, including residuals from the currently defined research studies, will be retained at the University of Wisconsin biobank. Protocol-specified studies should be clearly described and prioritized in the protocol, and in general, should not require additional review and approval. Investigators are encouraged to consult with the University of Wisconsin biobank for the evaluation of residual tissue specimens approaching depletion for protocol-specified studies.

6. TREATMENT PLAN

6.1 Agent Administration

Treatment will be administered on an outpatient basis. Body surface area (BSA) should be recalculated if ≥5% weight change. Reported adverse events and potential risks for MLN4924 (pevonedistat), carboplatin, and paclitaxel are described in Section 10. Appropriate dose modifications are described in Section 7. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Agent*	Dose	Route	Schedule	Cycle Length
Paclitaxel[#]	175 mg / m^2	IV infusion over 3 hours	Day 1	21 days (3 weeks)
Carboplatin[#]	AUC = 5**	IV infusion over 30-60 minutes***	Day 1	
MLN4924 (pevonedistat)	20 mg/m^2	IV infusion over 1 hour	Days 1, 3, 5	

[#]Suggested premedications are provided in section 6.1.3.1.
*Paclitaxel is administered first, followed by carboplatin, and then MLN4924 (pevonedistat).
**Doses and volume of diluent per institutional standard.
*** Rate of infusion may be per institutional standard.

Patients will receive 4 cycles of combination therapy with carboplatin, paclitaxel and MLN4924 (pevonedistat). After 4 cycles of combination therapy, the treating physician is given discretion whether to continue with a) carboplatin, paclitaxel and MLN4924 (pevonedistat), if clinical benefit, until progressive disease, unacceptable toxicity or patient desire to discontinue study therapy; or b) continue carboplatin and MLN4924 (pevonedistat) without paclitaxel, if clinical benefit, until progressive disease, unacceptable toxicity or patient desire to discontinue study therapy; or c) observe the patient on study. All patients will be followed for the duration of study and until resolution or stabilization of any adverse effects related to study therapy. If the patient is continued on a) or b), subsequent change to c) at later timepoints is also allowed.

6.1.1 MLN4924 (pevonedistat)

MLN4924 (pevonedistat) will be administered after paclitaxel and carboplatin at a dose of 20mg/m^2 on Days 1, 3 and 5. Day 1 should be administered on a Monday. For sites with the ability to administer Day 5 on Saturday, Day 1 may begin on Tuesday.

MLN4924 (pevonedistat) is to be administered as a 60-minute (±10 minutes) IV infusion, using a 250 mL D5W (5% dextrose in water) or normal saline (NS) IV bag through central or peripheral venous access. The drug can be diluted in 5% dextrose or normal saline to a final volume of 250mL. Infusion-related reactions have not been reported in the Pevonedistat program. If there is suspicion for any associated infusion-related reactions, 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 or normal saline immediately after IV administration is complete.

On Day 1 of each cycle patients will receive dexamethasone pre-medication per institutional standards for paclitaxel. Suggested pre-medications for Paclitaxel are outlined in Section 6.1.3.

Toxicity management should follow the guidelines and algorithms that are provided in Section 7.

If MLN4924 (pevonedistat) dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained. In each cycle, a maximum of 3 doses of MLN4924 (pevonedistat) should not be exceeded.

The amount of study drug to be administered will be based on body surface area (BSA). BSA will be calculated using a standard formula per institutional standards on Cycle 1 Day 1, and on Day 1 of subsequent cycles if the patient experiences a ≥5% change in body weight from the weight used for the most recent BSA calculation.

Pevonedistat may be continued as monotherapy if paclitaxel and carboplatin are discontinued.

6.1.2 Carboplatin

Carboplatin will be administered on Day 1 after the paclitaxel infusion is completed. Carboplatin at the appropriate dose will be given intravenously as a 30-60 minute infusion or per institutional standard in Dextrose 5% in Water or Sodium Chloride 0.9%, volume per institutional standard.

6.1.2.1 Carboplatin Dose Calculation and Administration

Carboplatin dose will be calculated using the Calvert formula:

Total Dose (mg) = target AUC* (GFR+25), GFR may be substituted by Creatinine Clearance (CrCl) calculation.

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

The CrCl 75 (replaces GFR in Calvert formula) will be calculated for each treatment course using the 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 a CrCl cap will be 125 mL/min. Questions about this calculation should be directed to the PI.

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

6.1.3 Paclitaxel

Paclitaxel should be diluted in Dextrose 5% or Sodium Chloride 09% per institutional standard and given by intravenous infusion. 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 3 hours via 0.22 micron in line filter and non-DEHP tubing. Solutions 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.

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.

6.1.3.1 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 injection, only when patients may have been non-adherent with oral pre-medication, in the investigator's opinion.

** 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.

Dexamethasone + 5-HT3 will not be repeated prior to carboplatin, unless clinically indicated.

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

6.2 General Concomitant Medication and Supportive Care Guidelines

Growth factor: the use of prophylactic growth factors should follow the American Society of Clinical Oncology (ASCO) guidelines and is not allowed prior to cycle 1, day 1. Growth factor may be administered after cycle 1 day 1, if patient meets indication per ASCO guidelines. 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.

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.

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.

For patient who develop an indication to start anticoagulation during study therapy (*i.e.,* a deep vein thrombosis (DVT) or pulmonary embolism (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.

Because there are potential drug-interactions 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. The Principal Investigator should be alerted if the patient is taking any drug known to affect or with the potential for drug interactions.

Paclitaxel is metabolized by CYP2C8 or CYP3A4. Use caution when administering with drugs that have pharmacokinetic interaction potential with these CYP-enzymes. Refer to the drug package insert for additional information on the potential drug-interactions.

Because the metabolic and excretion pathways of pevonedistat remain to be characterized in humans, the risk of DDIs between pevonedistat and concomitantly administered drugs is currently informed by available nonclinical and clinical data. On the basis of preliminary findings, administration of pevonedistat with moderate and strong CYP3A inhibitors and P-gp inhibitors is permitted. The effect of rifampin, a strong CYP3A inducer, on pevonedistat PK was evaluated in Study P1015. The result indicated that co-administration of rifampin did not result in clinically meaningful alteration of pevonedistat systemic exposures in the context of 28% of inter-individual variability in pevonedistat clearance. CYP3A inducers are no longer included in the list of excluded concomitant medications. The pevonedistat physiological based PK model indicates that the systemic exposure of pevonedistat was not sensitive to the perturbations of enzyme activity when the hepatic uptake becomes the rate-determining step of its clearance. Therefore, BCRP inhibitors are no longer included in the list of excluded concomitant medications. The study team should check a frequently-updated medical reference for a complete list of drugs to avoid. Patients will be provided with a Patient Drug Interactions Handout and Wallet Card (see Appendix B).

Table 2: Concomitant Medications Excluded During the Study

Therapy	**Comment/Exceptions**
Clinically significant metabolic enzyme inducers (see Appendix B)	Excluded.

Therapy	Comment/Exceptions
Any investigational agent other than MLN4924 (pevonedistat)	For example, androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag [Promacta], or romiplostim [Nplate] are excluded.
BCRP = breast cancer resistance protein, CYP = cytochrome C450	

6.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue beyond 4 cycles if the patient is deriving clinical benefit until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Clinical progression
- Patient non-compliance
- Pregnancy
    - All women of child bearing potential should be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period) at any time during study participation.
    - The investigator must immediately notify CTEP in the event of a confirmed pregnancy in a patient participating in the study.
- Termination of the study by sponsor
- The drug manufacturer can no longer provide the study agent

The reason(s) for protocol therapy discontinuation, the reason(s) for study removal, and the corresponding dates must be documented in the CRF.

6.4 Duration of Follow-Up

Patients will be followed for 5 years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dose Modifications for Toxicity

Patients must meet the following treatment parameters on Cycle 1 Day 1:

Parameter	Day 1	Day 3, 5
Absolute Neutrophil Count (ANC)	≥ 1,000/mcL	≥ 1000/mcL
Platelet Count	≥100,000/mcL	≥75,000/mcL
Total Bilirubin*	≤**1 x ULN** with exception of ≤**1.5 x ULN** direct bilirubin for patients with Gilbert's syndrome	≤**1 x ULN** with exception of ≤**1.5 x ULN** direct bilirubin for patients with Gilbert's syndrome
AST (SGOT)/ALT (SGPT)*	≤ 3.0 x ULN; ≤ 5 x ULN in setting of metastatic liver disease	≤ 3.0 x ULN; ≤ 5 x ULN in setting of metastatic liver disease
Creatinine	≤1.5 mg/dL or Cockcroft-Gault calculated clearance ≥ 30mL/min	N/A

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

All other toxicities (except alopecia, lymphopenia, hyperglycemia, hypoalbuminemia, fatigue, elevated serum alkaline phosphatase, neuropathy [see section 7.2.1], and hemoglobin [see section 7.1.3]) 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 in Section 7.

Qualifying laboratory tests can be obtained 24-72 hours before planned initiation of therapy as per study calendar (Section 11).

Dose holds and modifications are to 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) (version 5.0).

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 PI.

If a toxicity leads to 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 MLN4924 (pevonedistat) (*i.e.,* Day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

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 due to a specific toxicity to all protocol therapy at

least possibly related to study drugs will lead to removal of the patient from the study. If all treatment related toxicities do not recover within 3 weeks to the point where patients meet re-treatment criteria in Section 7.0 above, then patients should be removed from therapy on trial. If MLN4924 (pevonedistat) dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained. In each cycle, a maximum of 3 doses of MLN4924 (pevonedistat) should not be exceeded.

All dose reductions are permanent. Dose reductions are permitted until MLN4924 (pevonedistat) dose is 10mg/m^2. If untoward toxicity persists despite dose adjustments or if more than 2 dose reductions 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.

Pevonedistat may be continued as monotherapy in the event paclitaxel and carboplatin are discontinued.

Dose Modifications for Paclitaxel

Dose Modification Levels	Paclitaxel Dose
Dose level 1[#]	175 mg/m^2
Dose level -1	125 mg/m^2
Dose level -2	100 mg/m^2

[#]Starting dose

Dose Modifications for Carboplatin

Dose Modification Levels	Carboplatin Dose
Dose level 1[#]	AUC 5
Dose level -1	AUC 4
Dose level -2	AUC 3

[#]Starting dose

Dose modifications for MLN4924 (Pevonedistat)

Dose Modification Levels	MLN4924 (Pevonedistat) Dose
Dose level 1[#]	20 mg/m^2
Dose level -1	15 mg/m^2
Dose level -2	10 mg/m^2

[#]Starting dose

7.1.1 Neutrophils

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

Neutropenia**	**Management/Next Dose for MLN4924 (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.
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. Dose reductions are permitted for MLN4924 (pevonedistat) until dose is 10mg/m^2. 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 MLN4924 (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.

7.1.2 Platelets

Thrombocytopenia**	**Management/Next Dose for MLN4924 (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 ≥100,000. Resume at same dose level.	Hold dose until ≤ Grade 1. Resume at same dose level.	Hold until ≥100,000. Resume at same dose level.
Grade 3/4 ≤7 days and no clinically significant bleeding and > 10,000 mcL	Hold* until ≥100,000. Resume at same dose level.	Hold* until ≥100,000. Resume at same dose level.	Hold* until ≥100,000. Resume at same dose level.
Grade 4 lasting >7 days or requiring prophylactic platelet			

transfusion (≤10,000 mcL)			
1st episode	Hold* until ≥100,000. Reduce by 1 dose level.	Hold* until ≥100,000. Resume at same dose level.	Hold* until ≥100,000. Reduce by 1 dose level.
2nd episode	Hold* until ≥100,000. Reduce by 1 dose level.	Hold* until ≥100,000. Reduce by 1 dose level.	Hold* until ≥100,000. Reduce by 1 dose level.
Grade 3/4 of any duration with clinically significant bleeding ***	Off study	Off study	Off protocol
*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. Dose reductions are permitted for MLN4924 (pevonedistat) until dose is 10mg/m^2. 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 MLN4924 (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.			

7.1.3 Hemoglobin

Patients must have stable hemoglobin for ≥ 2 weeks prior to Cycle 1 Day 1. Supportive transfusion is permitted after Cycle 1 Day 1 and future cycles for subjects as clinically indicated per treating physician.

7.2 Dose Modifications for Non-Hematologic Toxicity

Patients must meet the following treatment parameters:

Parameter	Day 1	Day 3, 5
Creatinine	≤1.5 mg/dL or Cockcroft-Gault calculated clearance ≥ 30mL/min	N/A

7.2.1 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 MLN4924 (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. Resume 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. [#]After 4-6 cycles, paclitaxel may be discontinued per investigator discretion (including for neuropathy) and patient may continue on study.			

7.2.2 Arthralgia/Myalgia

Use CTCAE bone pain criteria for grading all arthralgias.

Arthralgia/Myalgia**	Management/Next Dose for MLN4924 (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	No change in dose	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 MLN4924 (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 4 mg BID) after chemotherapy. If symptoms recur despite this, the next dose of paclitaxel will be reduced by 1 dose level.

7.2.3 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 MLN4924 (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.			

Vomiting**	**Management/Next Dose for MLN4924 (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.

Vomiting**	**Management/Next Dose for MLN4924 (pevonedistat)**	**Management/Next Dose for Paclitaxel**	**Management/Next Dose for Carboplatin**
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.			

Diarrhea**	**Management/Next Dose for MLN4924 (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	Off study	Off study
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.			

7.2.4 Hepatic toxicity

There are no dose adjustments for carboplatin based on hepatic toxicity. Dose adjustments are for hepatoxicity at least possibly related to MLN4924 (pevonedistat) or paclitaxel.

AST and/or ALT**	**Management/Next Dose for MLN4924 (pevonedistat)**	**Management/Next Dose for Paclitaxel**
Grade 1-2	No change in dose	No change in dose
Grade 3		
Baseline 2.5-5x ULN and result <10x ULN	No change	No change
Baseline <2.5x ULN or result ≥10x 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.
Grade 4***	Off study	Off study
Bilirubin**	**Management/Next Dose for MLN4924 (pevonedistat)**	**Management/Next Dose for Paclitaxel**
Grade 1-2	No change in dose	No change in dose
Grade 3	Hold* until meeting treatment criteria and then reduce by 1 dose level.	Hold* until meeting treatment criteria and then reduce by 1 dose level.
Grade 4	Off study	Off study

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

**Patients requiring >2 dose reductions of chemotherapy should go off protocol therapy. Dose reductions are permitted for MLN4924 (pevonedistat) until dose is 10 mg/m^2. 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 MLN4924 (pevonedistat) during the cycle (*i.e*. Day 3 or 5), the dose will be skipped and the dose modification will be with the next scheduled dose.

*** Transient high elevations of AST/ALT have been seen in a small percentage of patients in early courses of MLN4924 (pevonedistat) dosing. This has been rapidly reversible and does not usually recur. If a grade 4 ALT/AST elevation reverses in 7 days or less, please contact PI to discuss whether it may be appropriate to continue on study, if patient is clinically benefitting, once treatment criteria met.

7.2.5 Hypersensitivity reaction

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

Hypersensitivity reactions to paclitaxel and/or carboplatin and/or pevonedistat 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 adverse event.

7.2.6 Other toxicities

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 MLN4924 (pevonedistat) and/or paclitaxel and carboplatin. If attribution for fatigue is at least possibly related to MLN4924 (pevonedistat), this agent alone should be reduced by one dose level. If attribution for fatigue is unlikely or unrelated to MLN4924 (pevonedistat), then the chemotherapy agent(s) with attribution of at least possible related should be reduced by one dose level.

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 MLN4924 (pevonedistat), paclitaxel and/or carboplatin, if attribution at least possibly related to drug.

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.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 10.1.

8.1 CTEP IND Agent

MLN4924 (pevonedistat) (NSC #793435)

Chemical Name: ((1S,2S,4R)-4-{(1S)-2,3-dihydro-1H-inden-1-ylamino]-7H-pyrrolo[2,3-d] pyrimidin-7-yl}-2-hydroxycyclopentyl) methyl sulfamate hydrochloride

Classification: NAE inhibitor

Other Names: TAK924/MLN4924; MLN4924-003 (hydrochloride salt); MLN4924-001 (free base); ML00644807; ML644507

CAS Registry Number: 905579-51-3 (free base); 1160295-21-5 (hydrochloride salt)

Molecular Formula: $C_{21}H_{26}ClN_5O_4S$

M.W.: 443.52 (free base); 479.98 (hydrochloride salt)

Mode of Action: MLN4924 (pevonedistat) is an inhibitor of 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.

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 pKa_1= 5.16 and = 8.81.

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 [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.

Preparation: Before use, bring MLN4924 (Pevonedistat HCl) vials to ambient room temperature (15º – 30º C / 59º – 86º F) for 15 minutes. Do not use a water bath to warm up the vials. Return vials to 2º – 8º C (36º – 46º 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

Compatibility: PVC or Polyolefin bags; non-DEHP IV bag is preferred but not required; BP Phaseal closed system transfer device, Spiros closed system transfer device.

Storage: Store MLN4924 (Pevonedistat HCl) refrigerated at 2º – 8º C (36º – 46º F) in its original carton to protect from light.

If a storage temperature excursion is identified, promptly return MLN4924 (Pevonedistat HCl) to 2º – 8º C (36º – 46º 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.

Stability: Stability studies of the intact vials are ongoing.

- Once MLN4924 (Pevonedistat) prepared IV solution is complete, the prepared IV solution must be used within 6 hours when stored at ambient room temperature. Discard the IV bag if it cannot be used within 6 hours.
- Alternatively, the prepared IV solution is stable up to 18 hours when stored at 2º - 8º C (36º – 46º F), after which the IV bag can be used within 3 hours upon removal from 2º - 8º C storage. The prepared IV solution must be brought up to ambient room temperature before administering to patient. If cannot used within 3 hours, the prepared IV solution must be discarded.

Route of Administration: Intravenous

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 normal saline or 5% dextrose in water immediately after IV administration is complete. Protecting IV bag from light during IV infusion is not required.

Potential Drug Interactions: *In vitro*, pevonedistat 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.

The geometric mean AUC from time 0 to infinity of pevonedistat in the presence of rifampin was 79% of that in the absence of rifampin (90% CI: 69.2%, 90.2%). The result indicated that co-administration of rifampin did not result in clinically meaningful alteration of pevonedistat systemic exposures in the context of 28% of inter-individual variability in pevonedistat clearance. Based on that, its exposure is unlikely to be affected by concomitant administration of CYP3A4 inducers.

In vitro, pevonedistat 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). Pevonedistat 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.

Pevonedistat is a substrate of P-gp and BCRP, and a weak inhibitor of P-gp, OATP and BCRP-mediated transport. Pevonedistat is unlikely to affect the PK of known P-gp, BCRP or OATP substrates. The pevonedistat PBPK model indicates that the systemic exposure of pevonedistat was not sensitive to the perturbations of enzyme activity when the hepatic uptake becomes the rate-determining step of its clearance. Considering the minimum effect on P-gp inhibition and hepatic uptake being the rate-determining step of pevonedistat clearance, the effect of BCRP inhibition is not expected to be clinically meaningful.

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.

Availability: MLN4924 (pevonedistat) is an investigational agent supplied to investigators by DCTD, NCI. MLN4924 (pevonedistat) is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13.3).

8.1.1 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.

Confirmation of patient enrollment onto study is required for initial supply. Submit agent requests through the PMB Online Agent Order Processing (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. 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.

8.1.1.1 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.

8.1.2 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.

8.1.3 Useful links and contacts

- CTEP Forms, Templates, Documents: https://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: https://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB OAOP application: https://ctepcore.nci.nih.gov/OAOP
- CTEP 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)

8.2 Commercial Agents

8.2.1 Carboplatin

Molecular Formula: $C_6H_{12}N_2O_4Pt$

M.W.: 371.25

Description: Crystalline powder

How Supplied: Carboplatin for injection is supplied as a sterile pyrogen-free powder in 10 mg/mL aqueous solution in multi-dose vials. Each vial contains 10 mg of carboplatin and water for injection. Carboplatin is commercially available from commercial sources.

Storage: Store un-reconstituted vials at 20-25 °C (68-77 °F) protected from light.

Preparation: Reconstitute with sterile water. Consult a carboplatin package insert for detailed formulation and storage instructions.

Administration: IV infusion over 15-60 minutes.

Agent Ordering: Carboplatin is commercially available.

For more detailed information, please consult a carboplatin package insert (Carboplatin Package Insert, 2011).

8.2.2 Paclitaxel

Molecular Formula: $C_{47}H_{51}NO_{14}$

M.W.: 853.9

Description: White to off-white crystalline powder.

How Supplied: Paclitaxel for injection is supplied as 6.0mg/mL aqueous solution in multi-dose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg purified Cremophor® EL (polyoxyethylated castor oil), and 49.7% (v/v) dehydrated alcohol. Paclitaxel is commercially available from commercial sources.

Storage: Store un-reconstituted vials at 20-25 °C (68-77 °F) protected from light.

Preparation: Consult a paclitaxel package insert for detailed formulation and storage instructions.

Administration: IV infusion over 3 hours.

Agent Ordering: Paclitaxel is commercially available.

For more detailed information, please consult a paclitaxel package insert (Taxol Package Insert, 2011).

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This is a single arm, two-stage study design with one interim analysis that will be used to evaluate the efficacy of the proposed MLN4924 (pevonedistat) /carboplatin/paclitaxel combination. The primary efficacy endpoint is the ORR. An ORR of 10% or less will be considered unacceptably low for this patient population. It is hypothesized that MLN4924 (pevonedistat) in combination with carboplatin and paclitaxel will result in an ORR of at least 30%. A two-stage Minimax design will be used to evaluate the ORR. In the first stage, 16 evaluable patients will be enrolled. If less than two patients have a response, then accrual will be terminated due to lack of efficacy. Otherwise, an additional evaluable 9 patients will be accrued for a total of 25 evaluable patients. This will test the null hypothesis that the ORR is 10% versus the alternative hypothesis that the rate is at least 30%. Assuming that the number of patients with an overall response is binomially distributed, this two-stage design has a significance of 10% and 90% power for detecting a response rate of 30%.

9.1.1 Definition of Primary Endpoint

The primary efficacy endpoint is ORR, which is defined as the proportion of evaluable subjects with a response. Response will be evaluated in this study using the new international criteria proposed by the revised RECIST guideline (Version 1.1). 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 the RECIST criteria. Patients will be re-evaluated for response every 6 weeks. The number and frequencies of responses will be summarized in tabular format. The ORR will be calculated and reported along with the corresponding 95% confidence interval which will be constructed using the Wilson score method.

9.1.2 Definition of Secondary Endpoints

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first. If a patient does not experience a progression or death event, then PFS will be censored as the last available disease assessment date. OS is defined as the duration of time from start of treatment to time of death. The overall survival time of patients still alive at the last follow-up assessment date will be censored. Toxicities and AEs will be evaluated by type and severity using the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

9.2 Sample Size/Accrual Rate

It is anticipated that the accrual of 25 patients will be completed within 18 months.

PLANNED ENROLLMENT REPORT

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	0	0	0	0	**0**
Asian	0	0	0	0	**0**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	1	1	0	0	**2**
White	11	12	0	0	**23**
More Than One Race	0	0	0	0	**0**
Total	**12**	**13**	**0**	**0**	**25**

PHS 398 / PHS 2590 (Rev. 08/12 Approved Through 8/31/2015) OMB No. 0925-0001/0002

9.3 Stratification Factors

N/A

9.4 Analysis of Secondary and Exploratory Endpoints

9.4.1 Analysis of Secondary Endpoints

PFS and OS will be analyzed using the Kaplan-Meier method. Median PFS and OS will be calculated along with the corresponding 95% confidence interval which will be constructed using the non-parametric Brookmeyer-Crowley method. All toxicities observed will be summarized in terms of types and severity. Toxicities will be tabulated and summarized by organ systems. Incidence rates of toxicities will be analyzed descriptively.

9.4.2 Analysis of Correlative Endpoints

NQO1 and *SCL7A11* expression levels will be summarized using standard descriptive statistics. Ratios of the Day 1 pre-treatment over the 6 hours post-infusion levels will be calculated and reported along with the corresponding 95% confidence intervals. A one sample t-test or Wilcoxon Signed Rank test will be used to evaluate changes from the Day 1 pre-treatment to the

6 hourspost-infusion assessment. A two-sample t-test or nonparametric Wilcoxon Rank Sum test will be used to compared changes in *NQO1* and *SLC7A11* expression levels from Day 1 pre-treatment to 6 hours post-infusion between responders and non-responders. Qualitative assessment of tumor NAE1 and UBC12 expression will be conducted by evaluating descriptive summaries of NAE1 and UBC12 expression levels. A linear mixed effects model with patient – specific random effects will be utilized to compared changes in γH2AX and RAD51 in CTCs at baseline and after treatment with MLN4924 (pevonedistat). *ATF3, B2M, GCLM, GSR, MAG1, RPLP0, SRXN1, TXNRD1*, and *UBC* expression levels will be summarized in terms of means, standard deviations, and ranges, stratified by assessment time point (pre-treatment and 6 hours post-infusion on Cycle 1, Day 1). Changes from the pre-treatment to post-infusion assessment will be evaluated using a paired t-test or nonparametric Wilcoxon Signed Rank test.

PK parameters will be summarized in terms of means, standard deviations, medians, and ranges, stratified by assessment time point. Changes in PK parameters between assessment time points will be evaluated using a paired t-test.

9.5 Reporting and Exclusions

9.5.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with MLN4924 (pevonedistat).

9.5.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ultimately deemed to be ineligible (identified after start of protocol therapy). Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the “unknown” status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, *etc.*). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 10.1) and the characteristics of an observed AE (Sections 10.2 and 10.3) will determine whether the event requires expedited reporting via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting.

10.1 Comprehensive Adverse Events and Potential Risks Lists (CAEPRs)

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.
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.

10.1.1 CAEPR for MLN4924 (pevonedistat)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
MLN4924 (Pevonedistat HCl, NSC 793435)

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)***
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)***

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%)**	
	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)***
	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.

10.1.2 Adverse Event List for Carboplatin

The most common adverse reactions for carboplatin are included below. See a carboplatin package insert for more information.

Myelosuppression, nausea, vomiting, diarrhea, weight loss, constipation, gastrointestinal pain, electrolyte imbalances, hypomagnesemia, hypocalcemia, hyponatremia, hyperuremia elevated alkaline phosphatase, AST, and total bilirubin,
peripheral neuropathies (mild paresthesias, clinical ototoxicity and other sensory abnormalities are rare),
renal tubular damage, renal insufficiency, impotence, sterility, amenorrhea, gynecomastia anaphylactoid and urticarial reactions (acute), flushing, rash, pruritis and rarely hypotension or bronchospasm,
alopecia, pain, asthenia and mucosal side effects, decreased serum electrolytes values (sodium, magnesium, calcium and potassium).

10.1.3 Adverse Event List for Paclitaxel

The most common adverse reactions for paclitaxel are included below. See a taxol package insert for more information.

Myelosuppression, nausea and vomiting, diarrhea, stomatitis, mucositis,
arrhythmia, heart block, ventricular tachycardia, hypotension, myocardial infarction (MI),
peripheral neuropathy, seizures,
anaphylactoid and urticarial reactions (acute), flushing, rash, pruritus,
alopecia, malaise, arthralgia, myalgia, elevated AST, alkaline phosphatase and bilirubin.
Note: Cardiac toxicities are rare and continuous cardiac monitoring is not required except for patients with serious conduction abnormalities or other underlying, serious cardiac risk factors.

10.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be utilized for AE reporting. 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/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent that are ***bold and italicized*** in the CAEPR (*i.e.*, those listed in the SPEER column, Section 10.1) should be reported through CTEP-AERS only if the grade is above the grade provided in the SPEER.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

10.3 Expedited Adverse Event Reporting

10.3.1 RAVE-CTEP-AERS Integration

The Cancer Therapy Evaluation Program 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.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Event form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct, and
- AEs are recorded and complete (no missing fields) and the form is query-free (fields added to the form during study build do not need to be query-free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and 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 AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 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 deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents > Education and Promotion, and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information > User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

10.3.2 Distribution of Adverse Event Reports

CTEP-AERS is programmed for automatic electronic distribution of reports to the following

individuals: Principal Investigator and Adverse Event Coordinator(s) (if applicable) of the Corresponding Organization or Lead Organization, the local treating physician, and the Reporter and Submitter. CTEP-AERS provides a copy feature for other e-mail recipients.

10.3.3 Expedited Reporting Guidelines

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Note: A death on study requires <u>both</u> routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Disease progression"** in the system organ class (SOC) "General disorders 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.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **<u>MUST</u>** immediately report to the sponsor (NCI) **<u>ANY</u>** 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 **<u>ANY</u>** 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).

<u>ALL</u> <u>SERIOUS</u> adverse events that meet the above criteria MUST be immediately reported to the NCI via electronic submission 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 submitted electronically 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 electronically 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

[2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

10.4 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during the trial using Medidata Rave. For this trial the Adverse Event CRF is used for routine AE reporting in Rave.

10.5 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of study drug must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

10.6 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported expeditiously via CTEP-AERS. Three options are available to describe the event:

Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
MDS
Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.7 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

11. STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week (7 days) prior to start of protocol therapy. Scans, x-rays, and ECHO/MUGA must be done ≤4 weeks (28 days) prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 72 hours prior to initiation of the next cycle of therapy.

		Cycle 1					Cycle 2			Cycle 3			Cycle 4+					
	Pre-study	Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	At disease progression	4 weeks after last dose of study drug[D]	Long term follow-up off study treatment[E]
MLN4924 (pevonedistat)[A]		X	X	X			X	X	X	X	X	X	X	X	X			
Carboplatin[B]		X					X			X			X					
Paclitaxel[C]		X					X			X			X					
Informed consent	X																	
Demographics	X																	
Medical history[F]	X																	
Interval history[G]	X	X	X	X			X			X			X			X	X	
Concurrent meds	X	X	X	X			X			X			X			X		
Physical exam[G]	X	X	X	X			X			X			X			X	X	
Vital signs[G]	X	X	X	X			X	X	X	X	X	X	X	X	X	X	X	
Height	X																	
Weight[G]	X	X	X	X			X			X			X			X	X	
Performance status[G]	X	X	X	X			X			X			X			X	X	
CBC w/differential and platelets	X	X	X	X	X	X	X			X			X			X	X	
Coagulation panel[H]	X																	
Chemistry panel[I, J]	X[I]	X[J]	X[J]	X[J]	X[J]	X[J]	X[I]	X[J]	X[J]	X[I]	X[J]	X[J]	X[I]	X[J]	X[J]	X[I]		
Pregnancy test[K]	X	X					X			X			X			X		
LVEF assessment by echocardiogram or radionuclide angiography	X																	
EKG[Q]	X															X	X	
Adverse event evaluation	X----------																	----------X
Tumor measurements	X									X						X		
Imaging[L]	X									X						X		

		Cycle 1					Cycle 2			Cycle 3			Cycle 4+					
	Pre-study	Day 1	Day 3	Day 5	Day 8	Day 15	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	Day 1	Day 3	Day 5	At disease progression	4 weeks after last dose of study drug[D]	Long term follow-up off study treatment[E]
Archival tissue collection[M]	X																	
Urinalysis[N]	X																	
Blood draw - PK analysis[P]		X																
Blood draw - CTCs		X								X						X		
Blood draw – NAE, NQO1, SCL7A11[O]		X																
Phone Follow-up																		X

A: MLN4924 (pevonedistat): 20 mg/m^2 over 60 minutes IV Days 1,3, and 5 of each cycle. Day 1 should be administered on Monday. Sites with the ability to administer Day 5 on Saturday may start Day 1 on Tuesday.

B: Carboplatin: AUC 5 IV on day 1 of each cycle

C: Paclitaxel: 175mg/m^2 IV on day 1 of each cycle

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

E: Subjects without documented disease progression will be followed for every 3 months for 1 year, then every 6 months until 5 years from end of treatment or until death. Once disease progression is documented, subjects will be followed every 3 months for 1 year, then every 6 months until 5 years from the time of documented progression or death.

F: 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.

G: At subsequent visits, symptom-directed history and physical examinations including vital signs, weight and performance status should be performed. Vital signs include diastolic and systolic blood pressure, heart rate, and body temperature. Vital sign measurements will be taken with the patient in the supine or sitting position.

H: To include PT and PTT

I: Complete chemistry panel will include BUN, creatinine, sodium, potassium, chloride, carbon dioxide, glucose, urate, total bilirubin, direct bilirubin, ALP, LDH, AST, ALT, albumin, magnesium, phosphate, and calcium. ALP, ALT, AST, and total bilirubin assessments **must** be performed and reviewed by the treating physician prior to each infusion of MLN4924 (pevonedistat).

J: Select chemistry panel to be completed on D1, 3, 5, 8, 15, of Cycle 1 and D3+5 of Cycles 2 and beyond will include BUN, creatinine, phosphate, total bilirubin, albumin, ALP, AST, and ALT. ALP, ALT, AST, and total bilirubin assessments **must** be performed and reviewed by the treating physician prior to each infusion of MLN4924 (pevonedistat).

K: Serum or urine pregnancy test (women of childbearing potential only) will be performed at least seven days before beginning study therapy. A negative serum or urine pregnancy test is also required at the beginning of each treatment cycle.

L: CT or MRI scans of chest, abdomen, and 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 chest, abdomen, and pelvis should occur after every 6 weeks (±7 days). If the pelvis CT scans are negative at baseline, they should be repeated as clinically indicated, however CT imaging of the chest and abdomen should occur every 6 weeks (±7 days).

M: Archival tissue collection is optional.

N: Urinalysis will be required at pre-study evaluation for all patients and then as clinically indicated. Urinalysis with microscopic analysis must be performed at screening. Urinalysis will include assessments of turbidity and color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, glucose, and leukocyte esterase. Urine microscopic analysis will include erythrocytes, leukocytes, bacteria casts, and crystals.

O: To be done on Cycle 1 Day 1 pre-treatment and 6h post-treatment with MLN4924 (pevonedistat).

P: To be collected on Cycle 1 Day 1 pre-infusion, immediately post infusion, and 3 hours ±5 minutes, 12 hours ±2 hours (optional), 24 hours ±2 hours, and 48 hours ±2 hours post-infusion

Q: To be performed pre-study, disease progression, end of treatment, and whenever medically necessary.

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, PT= prothrombin time, PTT=partial thromboplastin time, TSH=thyroid stimulating hormone.

Scheduled assessments every week are allowed a window of ±[3] days for Day 1 and ±[1] day for Days 3 and 5. A minimum of 1 full

calendar day between any 2 doses should be maintained 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.

12. MEASUREMENT OF EFFECT

12.1 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 new international criteria proposed by the revised RECIST guideline (Version 1.1). 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 the RECIST criteria.

12.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with MLN4924 (pevonedistat).

Evaluable for objective response. All patients who start the study treatment will be used in the primary calculation of the response rate. These patients will have their response classified according to the definitions stated below.

Evaluable Non-Target Disease Response. Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

12.1.2 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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). 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 [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm]

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.

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 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, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

12.1.3 Methods for Evaluation of Measurable 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 the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and 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 (≥1 cm) 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, Computerized Tomography (CT) is preferable.

Conventional CT and Magnetic Resonance Imaging (MRI) This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), 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 should 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.

Positron Emission Tomography (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 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.

Fluorodeoxyglucose (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 progressive disease (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.

12.1.4 Response Criteria

12.1.4.1 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 (<1 cm).

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 (0.5 cm). (Note: the appearance of one or more new lesions is also considered progressions).

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.

12.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

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

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 PI).

12.1.4.3 Evaluation of Best Overall Response

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

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-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

12.1.5 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.

12.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12.2 Other Response Parameters

Overall survival (OS) will be defined as time from study therapy initiation to death. Subjects who are still alive will be censored at the last follow-up.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 10 (Adverse Events: List and Reporting Requirements).

13.1 Study Oversight

This protocol is monitored at several levels, as described in this section. The Protocol Principal Investigator is responsible for monitoring the conduct and progress of the clinical trial, including the ongoing review of accrual, patient-specific clinical and laboratory data, and routine and serious adverse events; reporting of expedited adverse events; and accumulation of reported adverse events from other trials testing the same drug(s). At a minimum, a monthly conference call with participating sites will be conducted.

During the Phase 2 portion of this study, the Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

The Protocol PI will have, at a minimum, quarterly conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and pharmacovigilance. Decisions to proceed to the second stage of a Phase 2 trial will require sign-off by the Protocol Principal Investigator and the Protocol Statistician.

All Study Investigators at participating sites who register/enroll patients on a given protocol are responsible for timely submission of data via Medidata Rave and timely reporting of adverse events for that particular study. This includes timely review of data collected on the electronic CRFs submitted via Medidata Rave.

All studies are also reviewed in accordance with the enrolling institution's data safety monitoring plan.

13.2 Data Reporting

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 hold Rave CRA or Rave CRA (Lab Admin) role, site staff must hold a minimum of an AP registration type,

- To hold Rave Investigator role, the individual must be registered as an NPIVR or IVR, and
- To hold Rave Read Only role, site staff must hold an Associates (A) registration type.

If the study has a DTL, individuals requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff 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.

Site staff 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 in the Rave section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section 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.

13.2.1 Method

For studies assigned for **CTMS Routine** Monitoring:
This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Data will be submitted to CTMS at least once every two weeks via Medidata Rave (or other modality if approved by CTEP). Information on CTMS reporting is available at: http://www.theradex.com/clinicalTechnologies/?National-Cancer-Institute-NCI-11. On-site audits will be conducted on an 18-36 month basis as part of routine cancer center site visits. More frequent audits may be conducted if warranted by accrual or due to concerns regarding data quality or timely submission. For CTMS monitored studies, after users have activated their accounts, please contact the Theradex Help Desk at (609) 619-7862 or by email at CTMSSupport@theradex.com for additional support with Rave and completion of CRFs.

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the PI(s) at the site to ensure that all investigators at the ETCTN Sites understand the procedures for data submission for each ETCTN protocol and

that protocol specified data are submitted accurately and in a timely manner to the CTMS via the electronic data capture system, Medidata Rave.

Data are to be submitted via Medidata Rave to CTMS on a real-time basis, but no less than once every 2 weeks. The timeliness of data submissions and timeliness in resolving data queries will be tracked by CTMS. Metrics for timeliness will be followed and assessed on a quarterly basis. For the purpose of Institutional Performance Monitoring, data will be considered delinquent if it is greater than 4 weeks past due.

Data from Medidata Rave and CTEP-AERS is reviewed by the CTMS on an ongoing basis as data is received. Queries will be issued by CTMS directly within Rave. The queries will appear on the Task Summary Tab within Rave for the CRA at the ETCTN to resolve. Monthly web-based reports are posted for review by the Drug Monitors in the IDB, CTEP. Onsite audits will be conducted by the CTMS to ensure compliance with regulatory requirements, GCP, and NCI policies and procedures with the overarching goal of ensuring the integrity of data generated from NCI-sponsored clinical trials, as described in the ETCTN Program Guidelines, which may be found on the CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm) and CTSU websites.

An End of Study CRF is to be completed by the PI, and is to include a summary of study endpoints not otherwise captured in the database, such as (for phase 1 trials) the recommended phase 2 dose (RP2D) and a description of any DLTs. CTMS will utilize a core set of eCRFs that are Cancer Data Standards Registry and Repository (caDSR) compliant (http://cbiit.nci.nih.gov/ncip/biomedical-informatics-resources/interoperability-and-semantics/metadata-and-models). Customized eCRFs will be included when appropriate to meet unique study requirements. The PI is encouraged to review the eCRFs, working closely with CTMS to ensure prospectively that all required items are appropriately captured in the eCRFs prior to study activation. CTMS will prepare the eCRFs with built-in edit checks to the extent possible to promote data integrity.

CDUS data submissions for ETCTN trials activated after March 1, 2014, will be carried out by the CTMS contractor, Theradex. CDUS submissions are performed by Theradex on a monthly basis. The trial's lead institution is responsible for timely submission to CTMS via Rave, as above.

Further information on data submission procedures can be found in the ETCTN Program Guidelines (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm).

13.3 Data Quality Portal

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.

13.4 Collaborative Agreements Language

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) 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 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 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 NCI, 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 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 Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available 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:
Email : 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.

14. REFERENCES

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B 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 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.

- 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.

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)		**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 SEP/2020	
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

APPENDIX C ACCEPTABLE BIRTH CONTROL METHODS

<table>
<tr><th>Highly effective methods</th><th>Additional effective (barrier) methods</th></tr>
<tr><td>Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation. May be oral, intravaginal, or transdermal.</td><td rowspan="2">Male or female condom with or without spermicide (female and male condoms should not be used together)</td></tr>
<tr><td>Progestogen-only hormonal contraception associated with inhibition of ovulation. May be oral, injectable, or implantable.</td></tr>
<tr><td>Intrauterine device (IUD)</td><td rowspan="5">Cap, diaphragm, or sponge with spermicide</td></tr>
<tr><td>Intrauterine hormone-releasing system (IUS)</td></tr>
<tr><td>Bilateral tubal occlusion</td></tr>
<tr><td>Vasectomized partner</td></tr>
<tr><td>Sexual abstinence</td></tr>
</table>