NCT03772925

Phase 1 Study of MLN4924 (Pevonedistat) and Belinostat in Relapsed/Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome

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NCI Protocol #: 10246

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TITLE: A Phase 1 Study of MLN4924 (pevonedistat) and Belinostat in Relapsed/Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome

[redacted]

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VCU Massey Cancer Center
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[redacted]

[redacted]

NCI-Supplied Agent(s): MLN4924 (pevonedistat) (NSC 793435), Belinostat (NSC 726630)

IND #: 142135

IND Sponsor: DCTD, NCI

[redacted]

[redacted]

SCHEMA

This will be a two-part phase 1 dose-escalation and dose-expansion study of MLN4924 (pevonedistat) in combination with belinostat. Part A will be a 3+3 dose-escalation study of the combination to assess its safety and tolerability and identify a maximum tolerated dose (MTD)/recommended phase 2 dose (RP2D). Part B of the study will be a dose expansion study of 12 patients treated at the MTD/RP2D.

Dose Escalation Schedule				
Dose Level	**Belinostat**		**MLN4924 (pevonedistat)**	
	Dose (mg/m^2/day)	**Administration and Schedule**	**Dose (mg/m^2/day)**	**Administration and Schedule**
-1	800	Intravenously over 30 minutes once daily on Days 1-5 of each 21-day cycle	15	Intravenously over 60 minutes once daily on Days 1, 3, & 5 of each 21-day cycle**
1*	800		20	
2	800		25	
3	800		37	
4	1000		37	
5	1000		50	
6***	1000		59	

* Starting dose level

** When both drugs are given on the same day (Days 1, 3, 5), start the MLN4924 (pevonedistat) infusion within 60 mins after the completion of belinostat infusion.

*** The 59 mg/m^2 level will not begin until the NCI/CTEP, Principal Investigator and Takeda have closely examined the toxicity, PK and clinical data from the 50 mg/m^2 cohort. Takeda must give written approval for the 59 mg/m^2 to begin.

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OBJECTIVES

1.1 Primary Objectives

1.1.1 To identify the MTD/RP2D for a regimen combining MLN4924 (pevonedistat) with belinostat in patients with refractory/relapsed acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS).

1.2 Secondary Objectives

1.2.1 To describe the toxicities of this regimen.

1.2.2 To observe and record anti-tumor activity. Although the clinical benefit of these drug has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability.

1.2.3 [redacted]

1.2.4 To describe pharmacokinetic (PK) interactions, if any, between MLN4924 (pevonedistat) and belinostat.

[redacted]

2. BACKGROUND

2.1 Study Diseases

Despite considerable progress in elucidating the biology of AML in recent years, it continues to be a devastating disease (Cancer Genome Atlas Research, 2013). Over half of young adults and the vast majority of older adults with AML still die of their disease, and survival after relapse (or for those with refractory disease) is particularly dismal (Burnett *et al*., 2012; Roboz *et al*., 2014). In a recently reported international, randomized phase 3 clinical trial in 381 patients with relapsed/refractory AML, neither elacytarabine, a novel, elaidic acid ester of cytarabine, nor any of 7 commonly used AML salvage regimens provided clinically meaningful benefit to the patients, with low response rates and short overall and relapse-free survival (Roboz *et al*., 2014). The prognosis is uniformly poor for patients diagnosed at ages 60 years or older, who form the majority (Rowe *et al*., 2010), and those in whom AML develops secondary to prior chemotherapy or an antecedent hematologic disorder such as MDS or one of the myeloproliferative neoplasms (Dores *et al*., 2012). Patients with MDS who develop progressive or refractory disease after hypomethylating

agent therapy generally have a very poor outcome, and no approved interventions exist for these individuals (Garcia-Manero *et al*., 2014).

2.2 CTEP IND Agents

2.2.1 Belinostat

2.2.1.1 Background

Histone Deacetylase Inhibitors

DNA is wrapped around histone octamers known as nucleosomes, thereby forming a "beads on a string" structure, which folds into higher-order chromatin. Chromatin structure modifications are important modulators of the transcriptional activity of specific genes. Acetylation is one of the main histone modifications associated with the regulation of gene expression. Acetylation of the N-terminal lysine residues of histones leads to a more open chromatin configuration (euchromatin), which makes it more accessible to the transcription machinery (Bhalla, 2005). The 4 classes of human histone deacetylases (HDACs) mediate histone deacetylation, but also have several other substrates, including transcription factors (*e.g.,* p53, E2F, c-Myc, NF-κB, HIF-1α, RelA, GATA1, FoxO3A, YY1, Mad/Max, TFIIE, TFIIF), signaling mediators (*e.g.,* β-catenin, STAT 1 and 3), steroid receptors, chaperone proteins (*e.g.,* Hsp90), DNA repair enzymes (*e.g.,* Ku70, WRN), the nuclear import protein importin-α7, and the cytoskeletal protein α-tubulin (Bhalla, 2005; Lane and Chabner, 2009; Quintas-Cardama *et al*., 2011).

HDAC inhibitors (HDACi) exert multiple biological effects in cancer cells, including induction of differentiation/apoptosis, cell cycle/mitotic arrest, and autophagic cell death. Malignant cells possess higher levels of HDACs than normal tissues, and normal cells are relatively resistant to DNA damage and cell death induced by HDACi (Ungerstedt *et al*., 2005; Lee *et al*., 2010). As noted above, HDACi can modify gene expression secondary to acetylation of histones and by altering the acetylation status of transcription factors and other proteins involved in transcription. One of the most important HDACi-induced genes is the cyclin-dependent kinase inhibitor CDKN1A (p21WAF1/CIP1) (Richon *et al*., 2000). HDACi-induced increases in the level of this protein (Rosato *et al*., 2003), as well as that of p16 (CDKN2 or INK4) and p27, decreased expression of cyclins A and D, and dephosphorylation of retinoblastoma (Rb) protein, all contribute to HDACi-induced cell cycle arrest. HDACi also induce telomerase activity (Bhalla, 2005). HDACi acetylate histone H3K9 in pericentromeric chromatin, thus interfering with assembly of the kinetochore. This leads to mitotic arrest at prometaphase, followed by aberrant mitosis with chromosome segregation defects and ultimately apoptosis (Quintas-Cardama *et al*., 2011). Furthermore, HDACi lethality has been related to disruption of various cell cycle checkpoints (Warrener *et al*., 2003) as well as induction of mitotic slippage (Stevens *et al*., 2008).

HDACi activate both the intrinsic and extrinsic pathways of apoptosis. They increase levels of both Fas/Fas ligand and DR5/TRAIL (Insinga *et al*., 2005, Nebbioso *et al*., 2005) and down-regulate c-FLIP (Aron *et al*., 2003) in leukemic cells, but not in normal cells. HDACi increase levels of the pro-apoptotic Bcl-2 family proteins Bax, Bak, Bim (Chen *et al*., 2009), and Bmf; down-regulate the anti-apoptotic proteins Bcl-2, Bcl-xL, Mcl-1, XIAP (Rosato *et al*., 2006), and survivin; induce conformational change of Bax, and enhance the cleavage and subsequent activation of Bid (Bhalla,

2005; Quintas-Cardama *et al*., 2011; Ruefli *et al*., 2001).

HDACi induce DNA damage through increased generation of reactive oxygen species (ROS) (Rosato *et al*., 2003, Ruefli *et al*., 2001) and by impairing mechanisms of DNA repair (Bose *et al*., 2014). HDAC3 is essential for the maintenance of chromatin structure and genome stability (Bhaskara *et al*., 2010). HDACi decrease levels of the non-homologous end-joining (NHEJ) proteins Ku80 and Rad50 and acetylate Ku70 (Subramanian *et al.,* 2005), thereby decreasing its DNA binding. HDACi-mediated apoptosis is, in part, dependent on ROS generation, with subsequent DNA and mitochondrial damage and activation of the intrinsic apoptotic pathway (Bose *et al*., 2014). In addition, HDACi inhibit homologous recombination (HR) DNA repair (Kachhap *et al*., 2010). Recently, hypoacetylation of histone H3 lysine 56 has been shown to be necessary for efficient NHEJ (Miller *et al*., 2010), raising the possibility that HDACi may also disable this repair mechanism. Our group has shown that disabling certain cytoprotective pathways (*e.g*., NF-κB) promotes HDACi-mediated DNA damage and cell death in human leukemia cells (Dai *et al*., 2005).

Induction of autophagy is another important mechanism of cell death in response to HDACi (Robert *et al*., 2011; Shubassi *et al.,* 2012). Finally, HDACi, particularly HDAC6 inhibitors (Bali *et al.,* 2005), abrogate chaperone protein (Hsp90) function via hyperacetylation (Bhalla, 2005; Lane and Chabner, 2009; Quintas-Cardama *et al*., 2011). This leads to down-regulation, via polyubiquitinylation and proteasomal degradation, of misfolded Hsp90 client proteins such as Bcr-Abl (Nimmanapalli *et al*., 2003), FLT3, Akt, Raf (Bali *et al*., 2005) and checkpoint kinase 1 (Chk1) (Arlander *et al*., 2003; Brazelle *et al*., 2010). HDACi may also affect tumor cell survival by blocking tumor angiogenesis, and by inhibiting intracellular stress-response pathways (Lane and Chabner, 2009).

2.2.1.2 Clinical Experience with Belinostat

Belinostat (PXD101, Beleodaq, Spectrum Pharmaceuticals, Inc.), FDA-approved in 2014 for relapsed/refractory peripheral T-cell lymphoma (PTCL), is a hydroxamate derivative that inhibits both class I and II HDACs (pan-HDACi) (Molife *et al*., 2011). In preclinical studies, it suppresses the growth of and induces apoptosis in a variety of tumor types, both *in vitro* and *in vivo* (Plumb *et al*., 2003; Qian *et al*., 2006; Qian *et al*., 2008; Buckley *et al*., 2007; Ma *et al*., 2010). Although the drug has mostly been administered intravenously (IV) in clinical trials, an oral formulation has also been tested (Steele *et al*., 2011). IV belinostat displays linear PKs with respect to the maximum concentration (C_{max}) and the area under the "concentration time" curve (AUC) (Steele *et al*., 2008), without significant accumulation (Yeo *et al*., 2012). The intermediate elimination half-life is 0.3 to 1.3 hrs and independent of dose (Steele *et al*., 2008). Belinostat PKs are unaltered by concurrent administration with carboplatin and paclitaxel (Lassen *et al*., 2010). Glucuronidation by UGT1A1 is by far the major route of belinostat elimination in humans (Wang *et al.,* 2013). The drug has 5 major metabolites, which are not expected to have anticancer effects, and the parent drug and metabolites can be quantified in human plasma by means of a validated liquid chromatography-tandem mass spectrometry assay (Kiesel *et al*., 2013). *In vitro* studies indicate that belinostat is a weak/moderate inhibitor of cytochrome P450 family 2 subfamily C member 8 (CYP2C8) and a moderate to strong inhibitor of CYP2C9.

In a phase 1 study in patients with advanced solid tumors, the MTD of belinostat was 1000 mg/m^2

IV daily, administered over 30 minutes on Days 1-5 of a 21-day cycle (Steele *et al*., 2008). Dose-limiting toxicities (DLTs) included grade 3 fatigue, diarrhea, and atrial fibrillation, as well as grade 2 nausea/vomiting resulting in inability to complete a full 5-day cycle. A phase 1 study in patients with advanced hematologic neoplasms reported the same MTD (Gimsing *et al*., 2008). The most common treatment-related adverse events (AEs) (all grades) were nausea (50%), vomiting (31%), fatigue (31%), and flushing (31%). There was one case of grade 3 lymphopenia and two cases of grade 4 renal failure in the context of tumor lysis syndrome (TLS). The only related grade 3 events in more than one patient were fatigue and neurologic symptoms, and no cardiac events were noted. Oral belinostat was studied in 15 patients who were included in the phase 1 trial of IV belinostat in second or subsequent treatment cycles (Steele *et al*., 2011). High doses, up to 1000 mg/m^2 orally twice daily for 5 consecutive days, were found tolerable in this small study. In a phase 1 trial of oral belinostat in patients with lymphoma, the drug was found to be safe (no DLTs) at daily doses of 750-1250 mg on Days 1-14 every 3 weeks (Zain *et al*., 2009). In a phase 2 clinical trial, belinostat was administered IV at 1000 mg/m^2 daily on Days 1-5 every 21 days in patients with relapsed/refractory AML or newly diagnosed patients with AML over the age of 60 (Kirschbaum *et al.,* 2015). Belinostat was well tolerated; however, only 4 patients displayed SD for at least five cycles. A similar trial of belinostat at the same dose and schedule showed similar activity in myelodysplastic syndrome (MDS), with only one confirmed response (Cashen *et al*., 2012).

Belinostat has been found to be well tolerated in combination with carboplatin and paclitaxel in patients with solid tumors; in a phase 1 study, the maximal administered dose of belinostat was 1000 mg/m^2/d IV on Days 1-5 every 21 days, with carboplatin (AUC 5) and/or paclitaxel (175 mg/m^2) administered on Day 3 after belinostat (Lassen *et al*., 2010). Belinostat has also been evaluated in combination with 5-FU; cisplatin, doxorubicin, and cyclophosphamide (PAC, in advanced or recurrent thymic malignancies); cisplatin and etoposide; and 13-cis retinoic acid in phase 1 studies in patients with advanced solid tumors (Northfelt *et al*., 2007; Thomas *et al*., 2012; Balasubramaniam *et al*., 2013; Luu *et al*., 2013). In combination with a 96-hr infusion of 5-FU, 500 mg/m^2/d on Days 2-5, belinostat was well tolerated at doses up to 1000 mg/m^2 IV daily on Days 1-5 of a 21-day cycle (Northfelt *et al*., 2007). In combination with PAC (50/50/500 mg/m^2 IV every 3 weeks), the RP2D of belinostat was 1000 mg/m^2 over a 48-hr continuous IV infusion (Thomas *et al*., 2012). The RP2D of belinostat in combination with cisplatin 60 mg/m^2 on Day 1 and etoposide 80 mg/m^2/d on Days 1-3 of a 3-week cycle was 500 mg/m^2/24 h when administered by 48-hr continuous IV infusion (Balasubramaniam *et al*., 2013). In contrast, when combined with the non-cytotoxic 13-cis retinoic acid, 100 mg/m^2 daily on Days 1-14, the MTD of belinostat was not reached even at 2000 mg/m^2 daily on Days 1-5 every 21 days (Luu *et al*., 2013). The combination of belinostat, 1000 mg/m^2/d IV and azacytidine, 75 mg/m^2/d subcutaneously on Days 1-5 every 28 days has been found to be feasible and active in patients with advanced myeloid malignancies (Odenike *et al*., 2011). This dose of belinostat, administered on Days 1-5 and 8-12 of a 3-week cycle in conjunction with bortezomib (1.3 mg/m^2 on Days 1, 4, 8, and 11) was found to be tolerable and active (1 complete response [CR], 2 partial responses [PRs], and 8 who have stable disease [SD] of 22 evaluable patients) in a phase 1 trial in patients with relapsed/refractory acute leukemia or MDS (Holkova *et al*., 2012). In this trial, the CR was attained in a heavily pretreated patient with MLL-rearranged AML, while another patient with AML arising from JAK2-mutated myelofibrosis maintained SD for 2.5 years (Holkova *et al*., 2012).

2.2.2 MLN4924 (pevonedistat)

2.2.2.1 Background

2.2.2.1.1 Neddylation Inhibitors

The coordinated balance between synthesis and degradation of proteins is important in most cellular processes, and the ubiquitin-proteasome system (UPS) is responsible for much of the regulated protein turnover in the cell (Pevonedistat Investigator's Brochure, 2017). The UPS maintains cellular homeostasis and impacts many signaling pathways including cell cycle progression and regulation of transcription. This complex, multiprotein system involves distinct enzyme classes that coordinate ubiquitination and mediate ubiquitin-dependent degradation through the proteasome. The proteasome inhibitor (PI) bortezomib (Velcade; Millennium Pharmaceuticals, Inc.) has utility in the treatment of multiple myeloma and mantle cell lymphoma (Velcade Package Insert, 2015), suggesting that compounds targeting other components of the UPS could prove useful in the treatment of malignancies.

The polyubiquitination reaction involves the coordination of 3 classes of enzymes, E1 (ubiquitin activating), E2 (ubiquitin conjugating), and E3 (ligases) (Pevonedistat Investigator's Brochure, 2018). The E3 ligases are multiprotein complexes whose specificity is established by the members of the protein complex and whose activity is regulated by post-translational modification that include the addition of the ubiquitin-like molecule, neural precursor cell expressed, developmentally down-regulated 8 (NEDD8). NEDD8-activating enzyme (NAE) has been identified as an essential component of the NEDD8 conjugation pathway. The NEDD8 conjugation pathway controls the activity of a subset of UPS E3 ligases. Specifically, NEDD8 conjugation to cullin-dependent ubiquitin E3 ligases (CDLs) is necessary for their activity. These ligases control the timely ubiquitination and subsequent degradation of many proteins important for cell cycle progression (p27, cyclin E), DNA damage (Cdt-1), stress response (NRF-2, HIF1α), and signal transduction (phosphorylated IκBα).

MLN4924 (pevonedistat) (TAK-924, formerly MLN4924) is a first-in-class small molecule inhibitor of NAE under development for the treatment of malignancies (Pevonedistat Investigator's Brochure, 2018). Consistent with the inhibition of NAE, MLN4924 (pevonedistat) treatment of cultured tumor cells resulted in a decrease in NEDD8-cullin levels and a reciprocal increase in the levels of known CDL substrates, including NRF2 and CDT1, followed by cell death through apoptosis (Pevonedistat Investigator's Brochure, 2018). *In vitro* experiments with MLN4924 (pevonedistat) administered in combination with the hypomethylating agents azacitidine and decitabine demonstrated synergistic activity in AML cell lines. In nonclinical studies, treatment of cells with MLN4924 (pevonedistat) resulted in the accumulation of CDL substrates, followed by a DNA damage response and cell death. MLN4924 (pevonedistat) treatment resulted in tumor growth inhibition (TGI) in mouse tumor xenograft models of solid tumors, lymphoma, and acute myeloid leukemia (AML). These data indicate that inhibitors of NAE activity may be of therapeutic value in the treatment of various cancers, by preventing neddylation and activation of the CDLs, thus disrupting proteasomal degradation of a variety of critical regulatory proteins integral to tumor cell growth, proliferation, and survival.

2.2.2.2 Clinical experience with MLN4924 (pevonedistat)

There are 38 clinical studies of MLN4924 (pevonedistat) in patients with advanced malignancies.

To date, seven phase 1 MLN4924 (pevonedistat) studies have been completed: Study C15009 with azacitidine in patients with AML, Study C15010 with docetaxel, gemcitabine, or in combination with carboplatin and paclitaxel in patients with solid tumors, Study Pevonedistat-1012 assessing MLN4924 (pevonedistat) as a component of regimens with azacitidine in adult East Asian patients with AML or MDS, Study Pevonedistat-2001 with azacytidine in patients with HR MDS, CMML, and AML. Additionally, absorption, distribution, metabolism, and excretion properties of MLN4924 (pevonedistat) are being studied in Study Pevonedistat-1013 and two supportive phase I studies Pevonedistat-1014 (QTc interval) and Pevonedistat-1015 (effects of rifampin on PK of pevonedistat in patients with advanced solid tumors) (Pevonedistat Investigator's Brochure, 2021). A phase 1 study evaluating the effects of CYP3A-mediated inhibition on MLN4924 (pevonedistat) (Study C15011) has also completed enrollment. There are currently three ongoing studiesassessing MLN4924 (pevonedistat) as a component of regimens with azacitidine, in patients with HR MDS, CMML, or low-blast AML (Pevonedistat-3001) and in patients with newly diagnosed AML (Pevonedistat-2002), and HR MDS, CMML, and solid tumors (Pevonedistat-1016) (Pevonedistat Investigator's Brochure, 2021).

Study Pevonedistat-3001 is a phase 3, randomized, controlled, open-label study of pevonedistat and azacytidine versus single-agent azacitidine as first-line treatment for patients with HR MDS, CMML, or low-blast AML. Patients were randomized to the combination arm (pevonedistat and azacytidine) or single-agent azacytidine. Each cycle of treatment is 28 days. In the combination arm, patients received MLN4924 (pevonedistat) on Days 1, 3, and 5 at 20 mg/m^2. Azacitdine was administered in either the combination or single-agent arm on Days 1-5, 8, and 9 at 75 mg/m^2. A total of 443 patients have been treated. The study did not achieve statistical significance for the primary endpoint of event-free survival.

In a phase 1 study (C15001), MLN4924 (pevonedistat) was administered in four different dosing schedules to patients with non-hematological malignancies. Patients received MLN4924 (pevonedistat) on either 1) Days 1-5 at starting dose 25 mg/m^2 (Schedule A), 2) Days 1, 3, and 5 (with dexamethasone) at starting 50 mg/m^2 (Schedule B), 3) Days 1, 3, and 5 (without dexamethasone) at starting 50 mg/m^2 (Schedule C) or 4) Days 1, 8, and 15 at starting dose 147 mg/m^2 (Schedule D). Cycles were repeated every 21 days. A total of 62 patients were treated and DLTs included elevated LFTs, elevated bilirubin, elevated creatinine, hyperbilirubinemia, acute renal failure, and acute hepatic failure. The MTD for Schedule A & B was 50 mg/m^2 and the MTD was 67 mg/m^2 for Schedule C. The MTD for Schedule D was not determined.

In another phase 1 study (C15002), MLN4924 (pevonedistat) was administered IV to patients with lymphoma or multiple myeloma on 5 different dosing schedules (Schedule A: Days 1, 2, 8, and 9 at starting dose 25 mg/m^2; Schedule B: Days 1, 4, 8, and 11 at starting dose 110 mg/m^2; Schedule C: Days 1 and 8 at starting dose 110 mg/m^2; Schedule D: Days 1, 8, and 15 at starting dose 110 mg/m^2; Schedule E: Days 1, 4, 8, and 11 at starting dose 100 mg/m^2). Cycles were repeated every 21 days. A total of 56 patients were treated and DLTs experienced included febrile neutropenia,

elevated LFTs, muscle spasms, thrombocytopenia, and acute renal failure. The MTD for Schedule A was 110 mg/m^2 and for Schedule B the MTD was determined to be 196 mg/m^2. The MTD was not determined for Schedules C-E.

A phase 1 dose escalation study (C15003) of MLN4924 (pevonedistat) treated patients with acute myelogenous leukemia, high-grade myelodysplastic syndrome or acute lymphoblastic leukemia on 4 different dosing schedules (Schedule A: Days 1, 3, and 5 at starting dose 25 mg/m^2; Schedule B: Days 1, 4, 8 and 11 at starting dose 147 mg/m^2; Schedule C: Days 1, 8, and 15 at starting dose 44 mg/m^2; Schedule D: [MLN4924 (pevonedistat) starting dose of 45 mg/m^2 and azacytidine dose of 75 mg/m^2] Cycle 1: Days 1, 4, 11 and 15, with azacytidine on Days 8-12 and 15-16 of a 35-day cycle, Cycles 2+: Days 1, 4, 8, and 11, with azacytidine on Days 1-5 and 8-9 of a 28-day cycle; Schedule E: Days 1, 3, and 5, expansion cohort at a fixed dose of 50 mg/m^2). A total of 72 patients were treated and DLTs observed included elevated LFTs, hypotension, cardiac failure, GI necrosis, lactic acidosis, myocardial ischemia, renal failure and rash morbilliform. The MTD was established at 59 mg/m^2 for Schedule A and 83 mg/m^2 for Schedule B. The MTD was not determined for Schedules C-E.

A phase 1 study (C15005) assessing MLN4924 (pevonedistat) in adult patients with melanoma administered MLN4924 (pevonedistat) in 2 dosing schedules; Schedule A: Days 1, 4, 8, and 11 at starting dose of 50 mg/m^2 and Schedule B: Days 1, 8, and 15 at starting dose 157 mg/m^2. Cycles were repeated every 21 days. A total of 37 patients were treated but the study was closed early by the study sponsor. DLTs observed included hypophosphatemia, elevated creatinine, myocarditis, acute renal failure, and hyperbilirubinemia. The MTD determined for Schedule A was 209 mg/m^2 and the MTD was not determined for Schedule B.

A phase 1b dose escalation study (C15009) of MLN4924 (pevonedistat) plus azacitidine in naïve patients with acute myelogenous leukemia assessed safety and tolerability of the drug combination. Patients were dosed with (MLN4924) pevonedistat on Days 1, 3, and 5 at a starting dose of 20 mg/m^2 and azacitidine on Days 1-5, 8, and 9 at 75 mg/m^2. Cycles were repeated every 28-days. A total of 64 patients were treated and responses of CR, CRi and PR were observed in 58% of patients. The overall response rate in evaluable patients was 58% with a median response duration of 8.3 months. Responses were identified in all cytogenetic risk groups, *TP53* mutations, low and high marrow blast counts and in *de novo* as well as secondary AML.

A phase 1 dose escalation study of MLN4924 (pevonedistat) in advanced solid tumors administered MLN4924 (pevonedistat) in 3 dosing schedules: Schedule A: Days 1-5 at 50 mg/m^2 in a 21-day cycle, this schedule was subsequently discontinued due to severe hepatotoxicity. Schedule B: Days 1, 3, and 5 in a 21-day cycle at 50 mg/m^2 with 8 mg oral dexamethasone before each MLN4924 (pevonedistat) dose and Schedule C: Days 1, 3, and 5 in a 21-day cycle at 67 mg/m^2. On Schedule B and C, no Grade 3 or greater serious adverse events were noted.

There are 19 ongoing phase 1/1b studies assessing MLN4924 (pevonedistat) in patients with advanced solid tumors and hematologic malignancies.

In view of its single-agent activity and complementary mechanisms of action, MLN4924 (pevonedistat) may prove to be superior to PIs such as bortezomib in disabling NF-κB and

potentiating HDACi activity in relapsed/refractory AML or MDS.

2.3 Rationale

Multiple considerations support the argument that combining an NAE inhibitor such as MLN4924 (pevonedistat), with an HDACi could be effective in relapsed/refractory AML, based on reciprocal interactions. First, it exploits the NF-κB-inhibitory capacity of MLN4924 (pevonedistat) (Swords *et al*., 2010a) to disable an important HDACi compensatory cytoprotective response of AML cells (Dai *et al*., 2005). Importantly, NF-κB interruption diminishes AML leukemia-initiating cell (LIC) survival (Guzman *et al*., 2002). Moreover, both HDACi (Rosato *et al.,* 2003) and MLN4924 (pevonedistat) (Swords *et al*., 2010) induce oxidative injury and DNA damage in AML cells. Second, MLN4924 (pevonedistat)-induced DNA damage results in multiple DNA-damage checkpoint and repair processes (*e.g.,* Chk1 and Wee1 activation) (Blank *et al*., 2013), events known to be antagonized by HDACi (Brazelle *et al*., 2010). Thus, HDACis may reciprocally increase MLN4924 (pevonedistat) anti-leukemic activity by blocking DNA-damage responses (*e.g.,* checkpoint or DNA repair). Third, certain poor prognosis genetic aberrations (*e.g.,* p53 deficiency or FLT3-internal tandem duplication [FLT3-ITD]) are associated with impaired DNA checkpoints or repair (*e.g.,* defective HR) (Fan *et al*., 2010), which could render them particularly susceptible to this strategy. Finally, aside from PIs, MLN4924 (pevonedistat) is the first clinically relevant new-generation NF-κB antagonist available, and in sharp contrast to bortezomib, has significant anti-leukemic activity itself (Swords *et al*., 2010b). A model of proposed reciprocal interactions between NAE and HDACi is shown in Figure 1. In summary, MLN4924 (pevonedistat) blocks NF-kB and the intra-S-phase checkpoint in HDACi-treated cells; conversely, HDACis block checkpoints (Chk1/Wee1/ATR) and disrupt HR (Ladd *et al*., 2013) and NHEJ (Koprinarova *et al*., 2011) in malignant cells, leading to enhanced DNA damage and cell death.

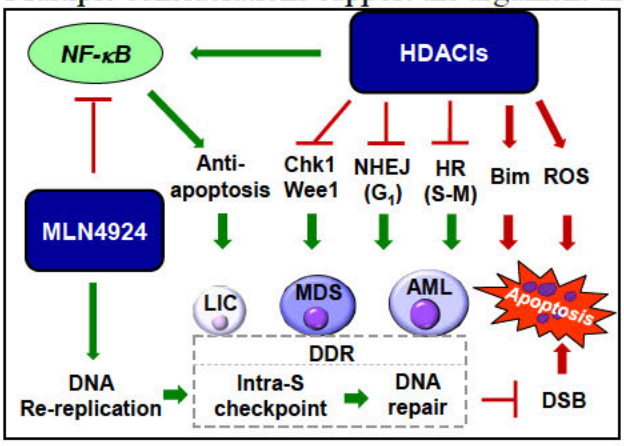


Figure 1. A hypothetical model summarizing mechanism of action underlying interactions between HDACis

In support of these concepts, we have very recently reported that MLN4924 (pevonedistat) and HDACi (*e.g.,* belinostat) interact in a highly synergistic manner in AML cells, particularly in p53 and/or FLT3-ITD mutant cells, as well as primary AML blasts (Zhou *et al*., 2016). Notably, the basis for synergism appears to be reciprocal in that MLN4924 (pevonedistat) inhibits NF-κB and disrupts the intra-S-phase checkpoint, events known to increase HDACi lethality. Conversely, HDACi block checkpoint (Wee1, Chk1) and repair (*e.g*., both HR and NHEJ) responses induced by MLN4924 (pevonedistat), and dramatically potentiate DNA damage. Moreover, similar interactions occurred in AML populations enriched for LICs (CD34+/CD38-/CD123+), but not in normal progenitors. Importantly, the MLN4924 (pevonedistat)/belinostat regimen very significantly increased survival in a systemic human xenograft AML model (MV4-11) while exerting minimal toxicity (*e.g.,* weight loss). The collective findings support further investigation of the MLN4924 (pevonedistat) and belinostat combination in AML.

As MLN4924 (pevonedistat) and belinostat have not been combined together in humans previously, a true assessment of toxicity is limited. Based on the available information, there is limited overlapping toxicity. Both drugs have evidence of hematologic toxicity including anemia and neutropenia which are generally acceptable toxicities in the AML population given the underlying pathology. While hepatic toxicity (elevated aspartate aminotransferase [AST]/ alanine aminotransferase [ALT]) was more common with MLN4924 (pevonedistat), it is less common with belinostat. Additionally, both drugs are associated with fever. Section 10.1 of the protocol provides a comprehensive list of known toxicities of each agent. The limited overlapping toxicity with known preclinical activity provides further support of investigation of the MLN4924 (pevonedistat) and belinostat combination in AML.

2.4 Correlative Studies Background

[redacted]

The following represent the candidate pharmacodynamic biomarkers, along with the assessment time-points and the objectives of our studies:

[redacted]

- [redacted]

[redacted]

[redacted]

HDACi increase the levels of pro-apoptotic [redacted]

[redacted]

- Pre- and post-treatment (6-hr) NAE inhibition in leukemic blasts

Preliminary data indicate that inhibitors of NAE activity may be of therapeutic value in a variety of cancers by preventing neddylation and activation of the CDLs, thus disrupting proteasomal degradation of a variety of critical regulatory proteins integral to tumor cell growth, proliferation, and survival. We will determine whether markers of NAE inhibition are present in leukemic blasts collected from patients approximately 6 hrs after receiving MLN4924 (pevonedistat) and belinostat.

2.5 Pharmacokinetic Studies Background

PK analysis of MLN4924 (pevonedistat) and belinostat will be performed with three goals: 1) to gain preliminary insights into potential PK interactions between the two agents; 2) to determine whether plasma drug levels can be achieved that mimic concentrations shown to be active in previous *in vitro* studies; and 3) to obtain preliminary information concerning correlations between PK parameters (*e.g.*, drug exposure) and results of pharmacodynamic studies and/or responses, if the latter occur.

See Section 5 for further details on operational characteristics of PK studies.

3. PATIENT SELECTION

3.1 Inclusion Criteria (all of the following criteria must be met for enrollment)

3.1.1 Patients must have one of the following, histologically or cytologically confirmed:

- AML (non- acute promyelocytic leukemia [APL] AML)
  - AML that is relapsed or refractory to at least one prior line of therapy
- MDS, must meet all of the following at the time of enrollment:
  - Higher risk MDS (intermediate-2 or high risk by the original IPSS) (Greenberg *et al*., 1997), and
  - Relapsed, refractory, or intolerant to at least one prior line of therapy containing a hypomethylating agent (DNA methyltransferase inhibitor).

3.1.2 Age ≥18 years.

Because no dosing or adverse event data are currently available on the use of MLN4924 (pevonedistat) in combination with belinostat in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.3 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).

3.1.4 Patients must have adequate organ and marrow function as defined below:

– total bilirubin	≤upper limit of normal (ULN) for the laboratory except in patients with Gilbert's syndrome. Patients with Gilbert's syndrome may enroll if direct bilirubin ≤1.5 x ULN for the laboratory of the direct bilirubin.
– AST(SGOT)/ALT(SGPT)	≤3 × institutional ULN.
– creatinine clearance	Within normal limits for the laboratory OR
– estimated glomerular filtration rate (GFR)	≥60 mL/min/1.73 m^2 appropriate to race for patients

with creatinine levels above institutional normal.

3.1.5 Known human immunodeficiency virus (HIV) positive patients who meet the following criteria will be considered eligible:
- CD4 count >350 cells/mm^3
- Undetectable viral load
- Maintained on modern therapeutic regimens utilizing non-CYP-interactive agents
- No history of Acquired Immune Deficiency Syndrome (AIDS)-defining opportunistic infections

3.1.6 If evidence of chronic hepatitis B virus (HBV) infection, HBV viral load must be undetectable on suppressive therapy, if indicated.

3.1.7 If history of hepatitis C virus (HCV) infection, patients must be treated and have an undetectable HCV viral load.

3.1.8 The effects of belinostat and/or MLN4924 (pevonedistat) on the developing human fetus are unknown. For this reason and because histone deacetylase inhibitors and NAE inhibitory agents are known to be teratogenic, women of child-bearing potential and men must use 1 highly effective method and 1 additional (barrier) method of contraception at the same time, from the time of signing the informed consent through 4 months after the last dose of study drug (female and male condoms should not be used together). Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, 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) and belinostat administration.

3.1.9 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) and/or family member available will also be eligible.

3.2 Exclusion Criteria (none of the following may be present for enrollment)

3.2.1 Clinical picture indicative of leukostasis or evidence of disseminated intravascular coagulopathy.

3.2.2 Uncontrolled coagulopathy or bleeding disorder.

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

3.2.4 Uncontrolled high blood pressure (*i.e.,* systolic blood pressure >180 mm Hg, diastolic blood pressure >95 mm Hg).

3.2.5 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).

3.2.6 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).

3.2.7 Ongoing toxicities ≥grade 2 from prior therapy, except those related to hydroxyurea (which is permitted through the first 5 days of study treatment).

3.2.8 APL (M3).

3.2.9 Active central nervous system (CNS) leukemia.

3.2.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to MLN4924 (pevonedistat) or belinostat.

3.2.11 Stem cell transplant within previous 3 months prior to initiation of study therapy.

3.2.12 Major surgical procedures ≤28 days before beginning study treatment or minor surgical procedures ≤7 days before beginning study treatment. No waiting required after placement of a vascular access device.

3.2.13 Uncontrolled intercurrent illness or infection.

3.2.14 Circulating blast count >50,000 mm^3 within 7 days preceding enrollment.

3.2.15 Current candidacy for a potentially curative allogenic stem cell transplant, unless declined.

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

3.2.17 Prolongation of the heart-rate corrected QT (QTc) interval ≥450 ms (*i.e.,* grade 1 or higher) on electrocardiogram (ECG) prior to initiation of study treatment.

- If baseline QTc on screening ECG is ≥450 ms (*i.e.,* grade 1 or higher):
  - Check potassium and magnesium serum levels, and
  - Correct any identified hypokalemia and/or hypomagnesemia and repeat ECG to confirm QTc interval.

- For patients with baseline heart rate <60 bpm or >100 bpm, manual measurement of QT interval by cardiologist is required, with Fridericia correction applied to that manual measurement to determine the QTc for eligibility consideration.

  Note: For patients with a heart rate of 60-100 bpm, manual measurement of QT interval and use of the Fridericia formula to determine QTc is NOT required.

3.2.18 Known cardiopulmonary disease defined as:

- Unstable angina;
- Congestive heart failure (New York Heart Association [NYHA] Class III or IV; see Appendix B);
- Myocardial infarction (MI) within 6 months prior to first dose (patients who had ischemic heart disease such as ACS, MI, and/or revascularization greater than 6 months before screening and who are without cardiac symptoms may enroll);
- Symptomatic cardiomyopathy;
- Clinically significant pulmonary hypertension requiring pharmacologic therapy
- Clinically significant arrhythmia defined as any of the following:
  - History of polymorphic ventricular fibrillation or torsade de pointes
  - Permanent atrial fibrillation (a fib), defined as continuous a fib for ≥ 6 months
  - Persistent a fib, defined as sustaining a fib lasting > 7 days and/or requiring cardioversion in the 4 weeks before screening
  - Grade 3 a fib defined as symptomatic and incompletely controlled medically, or controlled with device (*e.g.*, pace maker), or ablation in the past 6 months
  - Patients with paroxysmal a fib or < Grade 3 a fib for a period of at least 6 months are permitted to enroll provided that their rate is controlled on a stable regimen
  - Known congenital long QT syndrome.
  - Second degree atrioventricular (AV) block type II or third degree AV block
  - Ventricular rate <50 bpm or > 120 bpm.

3.2.19 Treatment with clinically significant metabolic enzyme inducers within 14 days before the first dose of the study drug.

Note: Because the lists of these agents are constantly changing, it is important to regularly consult a frequently-updated medical reference. As part of the enrollment/informed consent procedures, the patient will be counseled on the risk of interactions with other agents, and what to do if new medications need to be prescribed or if the patient is considering a new over-the-counter medicine or herbal product.

3.2.20 Ongoing or planned treatment with strong inhibitors of UGT1A1.

3.2.21 Any known *UGT1A* polymorphism, heterozygous or homozygous.

3.2.22 History of prior therapy with belinostat or MLN4924 (pevonedistat).

3.2.23 Active gastrointestinal (GI) conditions that might predispose to drug intolerance or poor drug absorption.

3.2.24 Known hepatic cirrhosis.

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

3.2.26 No other prior malignancy is allowed except for the following:

- *In situ* cervical cancer,
- Adequately treated basal cell or squamous cell skin cancer,
- Adequately treated Stage I or II cancer from which the patient is currently in complete remission, and
- Any other cancer from which the patient has been disease-free for at least 1 year.

3.2.27 Medical, psychological, or social condition that, in the opinion of the investigator, may increase the patient's risk, interfere with the patient's participation in the study, or hinder evaluation of study results.

3.2.28 Pregnant or nursing. Women of childbearing potential must have a negative serum pregnancy test performed within 7 days prior to the start of study therapy.

Note: Pregnant women are excluded from this study because MLN4924 (pevonedistat) is a NEDD8 inhibitor with the potential for teratogenic or abortifacient effects and because belinostat may cause teratogenicity and/or embryo-fetal lethality by virtue of targeting actively dividing cells. Because there is an unknown but potential risk for AEs in nursing infants secondary to treatment of the mother with MLN4924 (pevonedistat) or belinostat, breastfeeding should be discontinued if the mother is treated with MLN4924 (pevonedistat)/belinostat.

3.3 Inclusion of Women and Minorities

National Institutes of Health (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. [redacted]

Both men and women and members of all races and ethnic groups are eligible for this trial. Every attempt will be made to enter all eligible patients in this protocol to address the study objectives in a population representative of the population treated by the participating institutions.

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 [redacted] In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP), must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at [redacted]

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 such as the Roster Update Management System (RUMS), OPEN, Rave, acting as a primary site contact, or with consenting privileges,
- 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)	✔	✔	✔		
HSP/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:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol Principal Investigator on the IRB approval, and

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 can be found on the CTEP website at [redacted]

4.2 Site Registration

This study is supported by the NCI 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 [redacted] o 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 [redacted]

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 PO on the protocol. One

way to search for a protocol is listed below.

- Log on to the [redacted] 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-11030, and protocol number 10246,
- 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 #10246 Site Registration

- Site Initiation Visit
- 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.
  - [redacted]

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, go to the Regulatory section, and select Regulatory Submission.

[redacted]

4.2.4 Checking Site Registration Status

Site's registration status may be verified on the CTSU website.

- Click on *Regulatory* at the top of the screen,
- Click on *Site Registration*, and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with 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.
- 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.

[redacted] from the OPEN link on the CTSU members' website.

[redacted]

Patient enrollment for this study will be facilitated using the Slot Reservation System in conjunction with the registration system in OPEN. Prior to discussing protocol entry with the patient, all site staff must use the CTSU OPEN Slot Reservation System to ensure that a slot on the protocol is available to the patient. Once a slot reservation confirmation is obtained, site staff may then proceed to enroll the patient to this study.

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 Rave user roles: "Rave CRA" and "Rave CRA (Labadmin)" 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 in the Data Management section under the Rave Home tab and then under Rave Resource Materials.
- **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 5.2.

4.3.3 OPEN/IWRS Questions?

[redacted]

[redacted]

4.4 General Guidelines

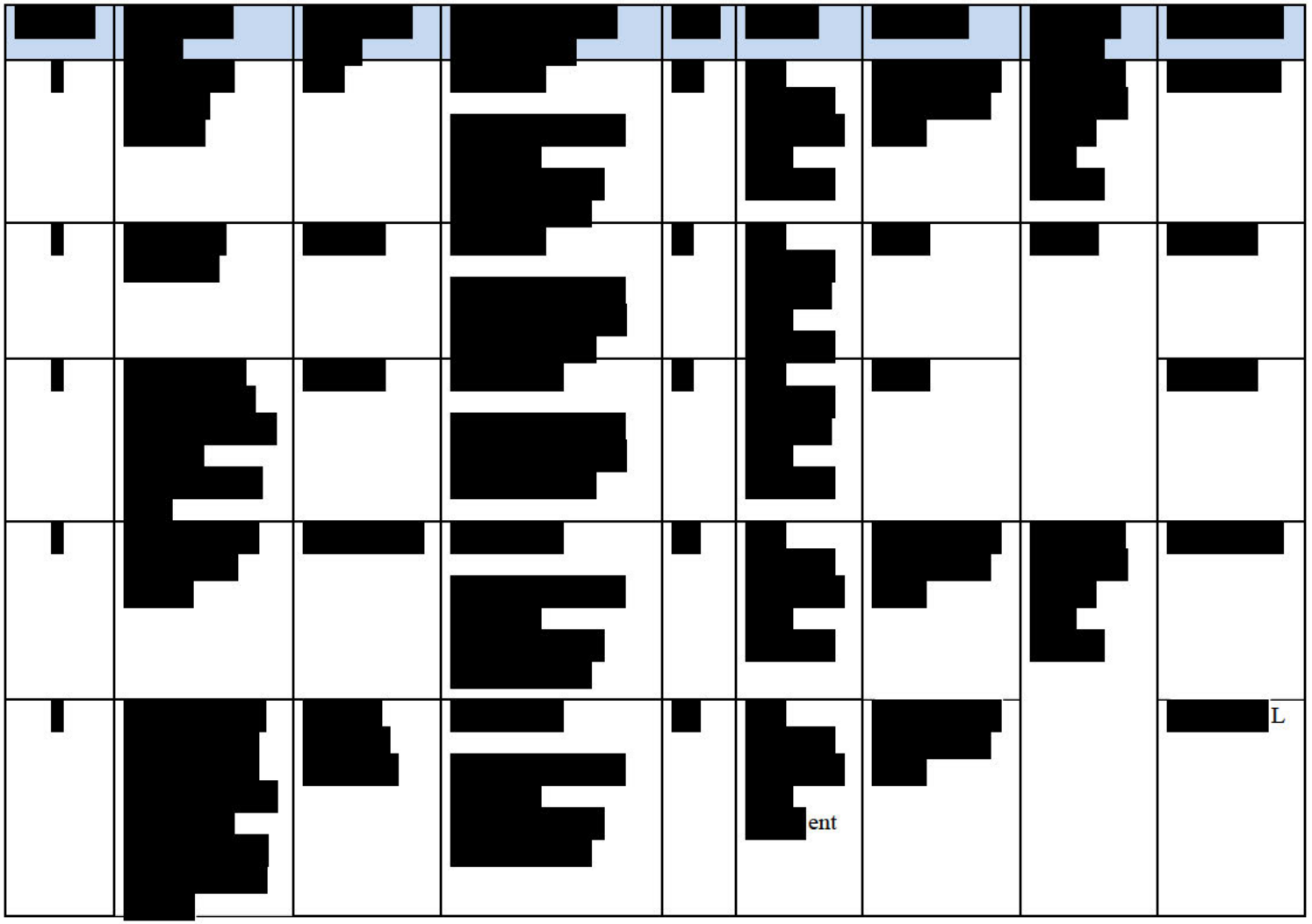
Participating sites are required to participate in a protocol-specific Site Initiation Teleconference prior to first patient registration.

Following registration, patients should begin protocol treatment within 7 to 14 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 PI and study coordinator should be notified of treatment delays and/or cancelations as soon as possible.

5. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

5.1 [redacted]



Priority	Biomarker Name	Biomarker Assay	Biomarker Type and Purpose	M/O	Timing	Specimen	Quantity Needed	Laboratory
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
7	Belinostat PK profile	PK profile	Integrated PK profiling	M	Cycle 1 Day 1-2: Belinostat sampling schedule[a]	Blood	5 mL	APC, Dr. Michelle Rudek, Johns Hopkins University
8	MLN4924 (pevonedistat) PK profile	PK profile	Integrated PK profiling	M	Cycle 1 Day 1-2: MLN4924 (pevoned-istat) sampling schedule[b]	Blood	5 mL	QPS, LLC

[a] See belinostat sampling schedule, Section 5.3.3.2.1.
[b] See MLN4924 (pevonedistat) sampling Section 5.3.3.1.1.
[c] Blood collection is mandatory provided that there are anticipated to be at least 10% blasts in the baseline sample (a determination made based on review of routine clinical CBC and differential). When blood is not anticipated to meet the 10% blast sampling threshold, and if an optional bone marrow is being done, collection of aspirate is allowed in lieu of blood sampling if the aspirate sample is anticipated to meet the 10% blast sampling threshold.
[d] Blood collection is mandatory provided that there are anticipated to be at least 40% blasts in the baseline sample (a determination made based on review of routine clinical CBC and differential). When blood is not anticipated to meet the 40% blast sampling threshold, and if an optional bone marrow is being done, collection of aspirate is allowed in lieu of blood sampling if the aspirate sample is anticipated to meet the 40% blast sampling threshold.

M=Mandatory, O=Optional, IHC=Immunohistochemistry, NCI=National Cancer Institute, PADIS= Pharmacodynamic Assay Development & Implementation Section, RT-PCR=reverse transcription polymerase chain reaction, VCU= Virginia Commonwealth University, CTRL=Clinical and Translational Research Laboratory, NGS=Next Generation Sequencing, PK=Pharmacokinetics, APC=Analytical Pharmacology Core laboratory

[redacted]

[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Specimen Collection Schedule

Biomarker	Specimen Type	Baseline time point(s)	C1D1 time point(s)	C1D2 time point(s)
PD-IHC	Blood or Bone Marrow Aspirate[a,b]	Pre-treatment		24hrs post-treatment[c]
PD-RTPCR	Blood	Pre-treatment	6hrs post-treatment	
PK-PEVO	Blood	Pre-treatment	See Section 5.3.3.1.1	
PK-BELINOSTAT	Blood	Pre-treatment	See Section 5.3.3.2.1	
PD-WB/FC	Blood or Bone Marrow Aspirate[a,b]	Pre-treatment		24hrs post-treatment[c]

[a] Bone marrow aspirate collection is optional and may be done in lieu of mandatory blood sampling, provided patient has consented to bone marrow aspirate sampling.
[b] Baseline blood or bone marrow aspirate samples for PD-IHC and PD-WB/FC should be anticipated to meet required blast percentage sampling threshold.
[c] Sample type collected post-treatment must be same as that collected pre-treatment

5.2 Specimen Tracking System Instructions

5.2.1 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 3
- 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.

For questions regarding the Specimen Tracking System, please contact the [redacted] at [redacted]

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

Submitted specimens may be labeled using the label-generation utility in STS or labels generated outside STS. Labels generated outside STS must contain information as outlined in applicable specimen handling sections.

5.2.2 Specimen Labeling

5.2.2.1 Blood and/or Bone Marrow Aspirate Specimen Labels

Please refer to handling section for each specimen type in Sections 5.3 and 5.4.

For Blood Labels generated through the STS:

- Patient Study ID
- Universal Patient ID (UPID)
- Specimen ID (automatically generated by Rave)
- Time point
- Specimen type (*e.g.*, blood, serum)
- Collection date, time, and specimen code (See Section 5.2.2.2) (to be added by hand)

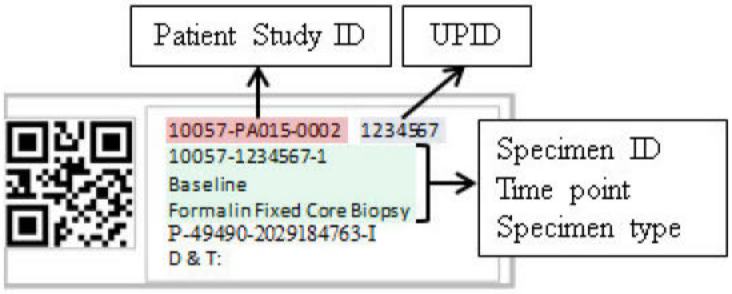
5.2.2.2 Specimen Code to Include on the Label:

Biomarker Name	Specimen code
[redacted]	[redacted]
Belinostat PK profile	PK-Belinostat
MLN4924 (pevonedistat) PK profile	PK-PEVO

IHC=Immunohistochemistry, RT-PCR=reverse transcription polymerase chain reaction, PD=pharmacodynamics, PG=pharmacogenetic, PK=pharmacokinetics, WB=western blot, FC=flow cytometry.

5.2.2.3 Example of Specimen Label (Generated through RAVE STS)

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.

5.2.3 Overview of Process at Treating Site

5.2.3.1 OPEN Registration

All registrations will be performed using the Oncology Patient Enrollment Network (OPEN) system. OPEN communicates automatically with the Interactive Web Response System (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 Patient Study ID and the Universal Patient ID, 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.

Registration with eligibility specimen analysis - *not applicable for this trial.*

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

5.2.4 Specimen Tracking System Overview and Enrollment Instructions

5.2.4.1 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 Sections 5.3 and 5.4.
- 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.

[redacted]

5.3.1.1 Collection of Specimen(s)

Paired samples of bone marrow aspirate (optional, from consenting patients) or blood will be collected when the baseline sample is anticipated to contain ≥10% blasts.

Collect paired (pre- and 24 hr post-treatment) samples of either blood (10 mL) or, from consenting patients, bone marrow aspirate (5 mL) in 10mL Streck tubes provided by the PADIS laboratory (see supply ordering information below). The same sample type (blood or bone marrow aspirate) must be used for both samples.

5.3.1.2 PADIS/Streck tube supply ordering

Prior to collection, e-mail a request for specimen collection and shipping materials to [redacted] Allow at least 6 business days for receipt of materials. A confirmation email with expected shipping date will be sent. Refer to the reference document "NCI-PADIS SOP for Streck Tube Samples" available on the CTSU website in the Supplemental Documents section for NCI-10246.

5.3.1.3 Handling of Specimen(s)

Samples may be held at room temperature until shipment on the day of collection. Samples being submitted to NCI-PADIS will be labeled as follows or labeled using the RAVE Specimen Tracking System.

Labels generated outside STS should mimic the STS labeling format as shown below:

- Patient ID: Protocol # (10246) - Treatment ID # (assigned at enrollment) – UPID (assigned in STS)
- Specimen ID: Protocol # (10246) - UPID plus sequentially generated integer (assigned in STS)
- Code: PD-IHC
- Type: Blood or Bone marrow
- Time Point: pre-dose or post-dose
- Date/time collected

5.3.1.4 Shipping of Specimen(s)

Specimens must be shipped at room temperature to the PADIS laboratory on the day of collection. The collected specimens are stable for up to 48 hours at room temperature (15˚C to 30˚C) prior to processing (per PADIS laboratory standards). Do not collect samples late in the day on Thursdays past the time in which it is possible to ship samples to PADIS for receipt on Friday morning and do not collect on Fridays, as PADIS is closed on Saturdays and Sundays. Also, do not collect and ship samples on the day before a federal holiday.

A sample inventory must accompany all shipments.

5.3.1.5 Site(s) Performing Correlative Studies

The NCI Pharmacodynamic Assay Development and Implementation Section (PADIS) laboratory will conduct this study.

5.3.2 RT-PCR of Pharmacodynamic Markers

RT-PCR will be performed to assess pharmacodynamic markers for drug response. The assay includes 2 integrated target genes: NQO1 and SLC7A11. Sampling for PD-RTPCR analysis is mandatory.

5.3.2.1 Collection of Specimen(s)

- Blood samples will be collected pre-treatment and 6 hr post-treatment. Collect 2.5 mL of blood in PAXgene RNA tube (see supply ordering information below).
- Ensure that the PAXgene tube is at room temperature (18°C–25°C) prior to use and properly labeled with patient identification.
- Using a blood collection set, collect blood into the PAXgene Blood RNA Tube using your institution's recommended standard procedure for venipuncture.
- Hold the PAXgene blood RNA tube vertically, below the donor's arm during blood collection.
- 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.

5.3.2.1.1 Asuragen/PAXgene tube supply ordering

Each participating site will procure PAXgene tubes. Recommended items/vendors include:

- BD Biosciences Catalog No. 762165: PAXgene® Blood RNA Tube 2.5mL
- Fisher Scientific Catalog No. 23-021-01 (Manufacturer No. 762165): BD PAXgene™ Blood RNA Tube 2.5mL
- QIAGEN Catalog No./ID 762125: PAXgene® Blood RNA Tube (IVD) 2.5mL

5.3.2.2 Handling of Specimen(s)

- Gently invert the PAXgene Blood RNA Tube 8 to 10 times.
- "Slow-freeze" the tube overnight at -20°C. The tube may then be transferred to a -70°C freezer for long-term storage.

Samples being submitted to Asuragen will be labeled as follows or labeled using the RAVE Specimen Tracking System.

Labels generated outside STS should mimic the STS labeling format as shown below:

- Patient ID: Protocol # (10246) - Treatment ID # (assigned at enrollment) – UPID (assigned in STS)
- Specimen ID: Protocol # (10246) – UPID plus sequentially generated integer (assigned in STS)
- Code: PD-RTPCR
- Type: Blood

- Time Point: pre or post
- Date/time collected

5.3.2.3 Shipping of Specimen(s)

[redacted]

5.3.2.4 Site(s) Performing Correlative Studies

This study will be conducted by Asuragen. Asuragen is a biotechnology company based in Austin, Texas involved in diagnostics and therapeutics. Asuragen's offerings include molecular diagnostic products providing identification of genetic abnormalities associated with oncology and genetic diseases.

5.3.3 Pharmacokinetic (PK) Studies

PK studies will be done to document PK findings and interactions, if any, between the study drugs. Sampling for PK analyses of both agents is mandatory.

Any circumstance which prevents collection, submission, or analysis of blood samples for PK studies should be reviewed with the principal investigator. PK samples will be collected, processed, and stored at the participating centers prior to shipment.

5.3.3.1 MLN4924 (pevonedistat) PK Studies

MLN4924 (pevonedistat) PK samples will be processed and shipped to QPS, LLC, for analysis.

5.3.3.1.1 Collection of Specimens MLN4924 (pevonedistat) Specimen(s)

- Whenever possible, collect PK specimens from a venous access point that has not been used for drug infusion, preferably using an 18G needle to avoid hemolysis.

- Collect 3 mL of venous blood into a **chilled** tube containing K2-EDTA (see tube ordering information below) at the time points specified below for MLN4924 (pevonedistat) PK analysis.
- GENTLY invert the tube 8-10 times to mix the additive with the collected blood prior to centrifugation and **place immediately on ice**.
- For MLN4924 (pevonedistat), sample collection will occur at these approximate time points on Cycle 1, starting on Day 1, timed from the **START** of the MLN4924 infusion:
  - pre-MLN4924 (pevonedistat) infusion
  - 30 minutes (±10 min) after the START of the MLN4924 (pevonedistat) infusion, and then
  - 1 hr (±10 min)
  - 2 hrs (±10 min)
  - 2.5 hrs (±10 min)
  - 5 hrs (±30 min)
  - 8 hrs (±45 min)
  - and 24hrs (± 4 hrs) after the START of MLN4924 (pevonedistat) infusion.

  Note: if samples cannot be obtained within the stated time point window, it's preferable to draw a sample as close to the time point as possible rather than omitting the sample – be sure the actual time of collection is recorded

5.3.3.1.1.1 MLN4924 PK supply ordering

Each participating site will procure K2-EDTA tubes. Recommended items/vendors include: BD (Becton Dickinson) Catalog No. 02-689-03 (Manufacturer No. BD367835): K2EDTA-containing plastic lavender-top tubes 3 mL

- Fisher Scientific Catalog No. 367835: K2EDTA-containing plastic lavender-top tubes 3 mL

5.3.3.1.2 Handling of MLN4924 (Pevonedistat) Specimen(s)

- Process **within 60 minutes** of collection.
- Centrifuge at approximately 1100 to 1300 × g (RCF) for 10 minutes 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.
- Immediately following centrifugation, gently remove plasma from the packed cells and transfer into 2 labeled 2 mL cryovials. Each plasma sample will be split into 2 cryovials, which should be clearly designated as part of "Set 1" (primary set) or "Set 2" (back-up set).
- To ensure a more homogeneous 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

- Samples being submitted to QPS will be labeled as follows or labeled using the RAVE Specimen Tracking System. Labels generated outside STS should mimic the STS labeling format as shown below:

    - Patient ID: Protocol # (10246) - Treatment ID # (assigned at enrollment) – UPID (assigned in STS)
    - Specimen ID: Protocol # (10246) - UPID plus sequentially generated integer (assigned in STS)
    - Code: PK-PEVO
    - Type: Blood
    - Time Point: pre or post
    - Date/time collected
    - Optional (not included in STS labels): “Set 1” or “Set 2”

- 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 should elapse between blood collection and freezing the plasma sample.
- Store samples frozen at approximately -70°C or lower until shipment.

5.3.3.1.3 Shipping of MLN4952 (Pevonedistat) Sample(s)

- Samples should be stored through the duration of the PK study and shipped as a batch by patient.
- The primary set of samples should be shipped using site supplies to the QPS laboratory within 3 months of first sample's collection date (*i.e.,* if baseline sample is collected on 06/01/2019, all of that patient's samples should be at the QPS laboratory by 09/01/2019). If a second set of patient samples can be batch shipped by waiting up to 2 weeks (*i.e.,* 3.5 months), this is allowed.
- Coordinate shipment with the QPS laboratory ([redacted] *via* email prior to shipment (on the day of shipment or before), providing the shipment tracking information and a copy of the sample inventory.
- All samples will be shipped *via* overnight express courier in insulated containers with enough dry ice to maintain the samples in a frozen state for at least 72 hours (3 days), or up to the expected delivery date, whichever is longer.
- Shipments should occur on Monday through Wednesday (Tuesday is the preferred day) except when the following day is a holiday.
- A sample inventory must accompany all shipments.

*Once receipt of the primary set of samples (SET 1) is confirmed by QPS, the back-up set of samples (SET 2) may be shipped.

[redacted]

5.3.3.1.4 Site Performing MLN4924 (pevonedistat) Correlative Studies

MLN4924 (pevonedistat) PK studies will be conducted by QPS, LLC.

5.3.3.2 Belinostat PK Studies

[redacted]

- Whenever possible collect PK specimens from a venous access point that has not been used for drug infusion.
- Collect 4-6 mL of venous blood into tubes containing sodium heparin (see tube ordering information below) at the time points specified below for belinostat PK analysis.
- GENTLY invert the tube 8-10 times after collection to avoid sample hemolysis.
- For belinostat, sample collection will occur at these approximate time points on Cycle 1, starting on Day 1, timed from the END of the belinostat infusion:
  - pre-belinostat infusion
  - 5 minutes (±1 min) prior to the END of belinostat infusion
  - 15 minutes (±10 min) after the END of the belinostat infusion and then
  - 30 minutes (±10 min)
  - 1 hr (±10 min)
  - 2 hrs (±10 min)
  - 4 hrs (±10 min)
  - 6 hrs (±30 min)
  - 8 hrs (± 45 min)
  - and 24 hrs (± 4 hrs) after the END of the belinostat infusion.

    Note: if samples cannot be obtained within the stated time point window, it's preferable to draw a sample as close to the time point as possible rather than omitting the sample – be sure the actual time of collection is recorded.

5.3.3.2.1.1 Belinostat PK supply ordering

Each participating site will procure sodium heparin tubes. Recommended items/vendors include:

- BD (Becton Dickinson) Catalog No. 23-021-017 (Manufacturer No. BD 367878): sodium heparin-containing plastic green-top tubes 6 mL
- Fisher Scientific Catalog No. 367878: sodium heparin-containing plastic green-top tubes 6 mL

5.3.3.2.2 Handling of Belinostat PK Specimen(s)

- Centrifuge at 2500-3000 rpm for 10 mins in swinging bucket (SW) or 15 mins in a fixed angle (FA) rotor at 4°C in a refrigerated centrifuge. Make sure that the centrifuge reaches speed and is maintained throughout the entire spin.
- Using a pipette, transfer equal aliquots of plasma into 2 labeled 2 mL cryovials, not exceeding ~1 mL per cryovial. Each plasma sample will be split into 2 cryovials, which should be clearly designated as part of "Set 1" (primary set) or "Set 2" (back-up set).
- Samples being submitted to APC will be labeled as follows or labeled using the RAVE Specimen Tracking System. Labels generated outside STS should mimic the STS labeling format as shown below:

    - Patient ID: Protocol # (10246) - Treatment ID # (assigned at enrollment) – UPID (assigned in STS)
    - Specimen ID: Protocol # (10246) - UPID plus sequentially generated integer (assigned in STS)
    - Code: PK-BELINOSTAT
    - Type: Blood
    - Time Point: pre or post
    - Date/time collected
    - Optional (not included in STS labels): "Set 1" or "Set 2"

- Freeze the plasma samples immediately at approximately ~70°C or below.
- Store samples frozen at approximately -70°C or lower until shipment.

5.3.3.2.3 Shipping of Belinostat PK Specimen(s)

- Samples should be stored through the duration of the PK study and shipped as a batch by patient (more than one patient/shipment is acceptable if the site has more than one patient on study).
- The primary set of samples should be shipped to the APC laboratory within 3 months of first sample's collection date (*i.e.,* if baseline sample is collected on 06/01/2019, all of that patient's samples should be at the APC laboratory by 09/01/2019). If a second set of patient samples can be batch shipped by waiting up to 2 weeks (*i.e.,* 3.5 months), this deviation is allowed.
- All samples should be shipped *via* overnight express courier in insulated containers with

enough dry ice to maintain the samples in a frozen state.

- [redacted]

[redacted]

[redacted]

5.3.3.2.4 Site Performing Correlative Studies

Belinostat PK studies will be conducted by the [redacted] under the direction of Michelle A. Rudek, [redacted] is a well-recognized expert in pharmacokinetics who is also a member of the Investigational Drug Steering Committee of NCI/CTEP. She is the director of the APC laboratory. She has published extensively in pharmacokinetic studies of investigational agents, including in rational combination, and performed pharmacokinetic analysis of belinostat in a recently completed CTEP/ET-CTN trial of belinostat in combination with the Wee1 inhibitor AZD1775 in patients with relapsed/refractory AML or high-risk MDS. MLN4924 (pevonedistat) PK studies will be performed by QPS as per Takeda.

Belinostat will be measured in plasma using validated liquid chromatography-tandem mass spectrometry methods (Kiesel *et al.,* 2013; Xu *et al.,* 2012). Plasma concentration versus time data for belinostat and metabolites will be analyzed non-compartmentally or compartmentally using Phoenix WinNonlin. PK parameters for exposure (C_{max}, C_{min}, and AUC) along with $T_{1/2}$ and V_d will be assessed.

[redacted]

[redacted]

[redacted]

[redacted]

5.4.1.1 Collection, Handling, Shipping of PD-WB/FC Specimen(s)

Samples may be collected, handled and shipped in 1 of 2 ways (using the "routine approach" or the "alternative approach"), as shown below. The "routine approach" requires that the samples be immediately processed to mononuclear cell suspensions or pellets at the site where collected, followed by frozen storage and subsequent shipment to VCU CTRL. The "alternative approach" is outlined for sites without capabilities for immediate mononuclear cell isolation and requires that the sample be collected in specialized tubes followed by overnight shipment to VCU CTRL on the day of collection.

5.4.1.2 **Routine Approach** – Collection, Handling, Shipping of PD-WB/FC Specimen(s)

5.4.1.2.1 **Routine Approach** – PD-WB/FC Sample Collection

Paired samples of bone marrow aspirate (optional, from consenting patients) or blood will be collected from all consenting studies when the baseline sample is anticipated to contains ≥10% blasts.

Collect paired (pre-treatment and 24 hr post-treatment) samples of either peripheral blood (10 mL) or, optionally from consenting patients, bone marrow aspirate (5 mL) in tubes containing K2-EDTA (see tube ordering information below). The same

sample type (blood or bone marrow aspirate) must be used for both samples.

5.4.1.2.1.1 **Routine Approach** – PD-WB/FC supply ordering

Each participating site will procure K2-EDTA tubes. Recommended items/vendors include:

- BD (Becton Dickinson) Catalog No. 02-689-03 (Manufacturer No. BD367835): K2EDTA-containing plastic lavender-top tubes 3mL
- Fisher Scientific Catalog No. 367835: K2EDTA-containing plastic lavender-top tubes 3mL

5.4.1.2.2 **Routine Approach** – PD-WB/FC Handling of Specimens(s)

Samples will be processed within 2 hours of collection for isolation of leukemic mononuclear cells in a uniform manner, using BD Phosflow lyse/fix red cell lysis buffer (BD Bioscience), by dedicated research personnel according to manufacturer-specified protocol. Briefly, samples will be depleted of red blood cells by incubation with the buffer. After washing and counting, the cells will be resuspended in FBS/10% DMSO solution (5×10^6 cells/mL) in cryovials, frozen using a controlled-rate freezing apparatus or isopropanol chamber, and stored at -80°C.

Samples being submitted to VCU CTRL will be labeled as follows or labeled using the RAVE Specimen Tracking System. Labels generated outside STS should mimic the STS labeling format as shown below:

- Patient ID: Protocol # (10246) - Treatment ID # (assigned at enrollment) – UPID (assigned in STS)
- Specimen ID: Protocol # (10246) - UPID plus sequentially generated integer (assigned in STS)
- Code: PD-WB/FC
- Type: Blood or Bone marrow
- Time Point: pre or post
- Date/time collected
- Additional field for all labels (STS-generated or generated outside STS): Cell count or cell concentration in sample

5.4.1.2.3 **Routine Approach** – PD WB/FC Shipping of Specimen(s)

The frozen cell suspension may be temporarily stored, and then shipped by overnight courier on dry ice to the Clinical and Translational Research Laboratory (CTRL) at the VCU Massey Cancer Center for western blot and/or flow cytometry analysis. Based on preliminary experiments, we have concluded that shipping frozen cell pellets does not adversely affect western blot or flow cytometry results as compared to analyzing fresh samples.

Samples must be paired (baseline samples without post-treatment samples should not be submitted). All complete sample sets for each patient (pre- and post-treatment) must be shipped on dry ice by overnight courier.

If a patient consented to both PD-WB/FC and pharmacogenomic (PG) sampling, the frozen PG cell pellet(s) may be batched for submission to the CTRL along with the frozen pharmacodynamic cell suspensions. A sample inventory must accompany all shipments.

Coordinate shipment and arrival dates with [redacted] by phone or email prior to shipment. Plan to ship on Monday through Thursday only. Do not ship samples for arrival on a holiday or weekend. Contact [redacted] in advance if any questions arise about timing of shipments.

[redacted]

5.4.1.3 **Alternative Approach** – Collection, Handling, Shipping of PD-WB/FC Specimen(s)

5.4.1.3.1 **Alternative Approach** – PD-WB/FC Sample Collection

Paired samples of bone marrow aspirate (optional, from consenting patients) or blood will be collected from all consenting studies when the baseline sample is anticipated to contains ≥10% blasts.

Collect paired (pre-treatment and 24 hr post-treatment) samples of either peripheral blood (10 mL) or, optionally from consenting patients, bone marrow aspirate (5 mL), in Cyto-Chex® BCT tube(s) (see tube ordering information below). The same sample type (blood or bone marrow aspirate) must be used for both samples.

5.4.1.3.1.1 **Alternative Approach** – PD-WB/FC supply ordering

As needed, each participating site will procure Cyto-Chex® BCT tubes (if opting to use the Alternative Approach to WB/FC sampling). Recommended items/vendors include:

- Streck Catalog No. 213361: Cyto -Chex® BCT tubes 5mL (6-tube pack); 25 and 100 tube packs also available from Streck

- Fisher Scientific Catalog No. 11-716-357 (Streck213361): Cyto-Chex® BCT tubes 5mL (6-tube pack); 25 tube pack also available from Fisher

5.4.1.3.2 **Alternative Approach** – PD-WB/FC Handling of Specimens(s)

Samples may be held at room temperature until shipment on the day of collection.

Samples being submitted to VCU CTRL will be labeled as follows or labeled using the RAVE Specimen Tracking System. Labels generated outside STS should mimic the STS labeling format as shown below:

- Patient ID: Protocol # (10246) - Treatment ID # (assigned at enrollment) – UPID (assigned in STS)
- Specimen ID: Protocol # (10246) - UPID plus sequentially generated integer (assigned in STS)
- Code: PD-WB/FC
- Type: Blood or Bone marrow
- Time Point: pre or post
- Date/time collected

5.4.1.3.3 **Alternative Approach** – PD-WB/FC Shipping of Specimen(s)

Samples will be shipped at room temperature by overnight courier, preferably for morning delivery, to the VCU CTRL laboratory on the day it is collected. The collected samples are stable for up to 48 hours at room temperature (15˚C to 30˚C) prior to processing.

A sample inventory must accompany all shipments.

Coordinate shipment and arrival dates with [redacted] by phone or email prior to shipment. Plan to ship on Monday through Thursday only. Do not ship samples for arrival on a holiday or weekend. Contact [redacted] in advance if any questions arise about timing of shipments.

[redacted]

5.4.1.4 Site(s) Performing Correlative Studies

[redacted]

5.4.2 Pharmacodynamic Studies (RT-PCR analysis)

[redacted] See section 5.3.2 for information regarding specimen collection, handling, and shipping, as well as the site performing the correlative study. Sampling for PD-RTPCR analysis is mandatory.

5.4.3 PG Studies

[redacted]

5.4.3.1 Collection of Specimen(s)

- A single baseline sample of bone marrow aspirate (if patient consents to bone marrow sampling) or blood will be collected when the sample is anticipated to contain ≥40% blasts.
- Collect a single pre-treatment sample of bone marrow aspirate (2.5 mL) or blood (5 mL) into a tube containing sodium heparin (see tube ordering information below).

5.4.3.1.1 PG supply ordering

Each participating site will procure sodium heparin tubes. Recommended items/vendors include:

- BD (Becton Dickinson) Catalog No. 23-021-017 (Manufacturer No. BD 367878): sodium heparin-containing plastic green-top tubes 6mL
- Fisher Scientific Catalog No. 367878: sodium heparin-containing plastic green-top tubes 6mL

5.4.3.2 Handling of Specimens(s)

Samples will be processed within 2 hours of collection for isolation of leukemic mononuclear cells in a uniform manner using Ficoll-Hypaque by dedicated research personnel according to manufacturer-specified protocol. After washing twice with PBS, 1 x 10^6 cells/mL will be

aliquoted into one cryovial and remaining cells in another cryovial. Cells will be flash frozen in liquid nitrogen and stored at -80°C as a cell pellet.

Samples being submitted to VCU CTRL will be labeled as follows or labeled using the RAVE Specimen Tracking System. Labels generated outside STS should mimic the STS labeling format as shown below:

- Patient ID: Protocol # (10246) - Treatment ID # (assigned at enrollment) – UPID (assigned in STS)
- Spec ID: Protocol # (10246) - UPID plus sequentially generated integer (assigned in STS)
- Code: PG
- Type: Blood or Bone marrow
- Time Point: pre
- Date/time collected
- Cell count or cell concentration in final cell pellet

5.4.3.3 Shipping of Specimen(s)

The cell pellet(s) may be temporarily stored and then shipped by overnight courier on dry ice to [redacted] If samples are collected for both PD-WB/FC and PG, the frozen PG cell pellet(s) may be batched for submission to the VCU CTRL along with the frozen PD-WB/FC cell suspensions.

Use shipment instructions from Section 5.3.1.3. A sample inventory must accompany all shipments.

5.4.3.4 Site(s) Performing Correlative Study

VCU Department of Pathology Division of Molecular Diagnostics, Richmond, VA will conduct this study. [redacted] is an expert in genetic profiling, has collaborated on multiple pre-clinical studies involving NGS profiling of leukemic specimens, and is a co-investigator on [redacted] Leukemia and Lymphoma Society award (as well as an R01 award) in which she is specifically responsible for NGS patient profiling.

[redacted]

Results of all analyses will be provided to the principal investigator, senior scientist, and

coordinating study team as available or as requested.

6. TREATMENT PLAN

6.1 Agent Administration

This will be a two-part phase 1 dose-escalation and exploratory dose-expansion study of MLN4924 (pevonedistat) in combination with belinostat. Part A will consist of a 3+3 dose-escalation phase of the combination to assess its safety and tolerability and identify an MTD/tentative RP2D. After the MTD has been established, Part B of the study will involve an exploratory-dose expansion study of 12 additional patients who will be enrolled at the tentative RP2D to gain further insights into the safety of the regimen. MLN4929 (pevonedistat) and belinostat dose rounding is allowed per institutional guidelines.

Treatment will be administered on an outpatient basis. Cycles are to be repeated every 21 days. Reported adverse events and potential risks are described in Section 10. Appropriate dose modifications are described in Section 7. Other than hydroxyurea during the first 5 days of study treatment, no investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Dose Escalation Schedule				
Dose Level	**Belinostat**		**MLN4924 (pevonedistat)**	
	Dose (mg/m^2/day)	**Administration and Schedule**	**Dose (mg/m^2/day)**	**Administration and Schedule**
-1	800	Intravenously over 30 minutes once daily on Days 1-5 of each 21-day cycle	15	Intravenously over 60 minutes once daily on Days 1, 3, & 5 of each 21-day cycle**
1*	800		20	
2	800		25	
3	800		37	
4	1000		37	
5	1000		50	
6***	1000		59	

* Starting dose level

** When both drugs are given on the same day (Days 1, 3, 5), start the MLN4924 (pevonedistat) infusion within 60 mins after the completion of belinostat infusion.

*** The 59 mg/m^2 level will not begin until the NCI/CTEP, Principal Investigator and Takeda have closely examined the toxicity, PK and clinical data from the 50 mg/m^2 cohort. Takeda must give written approval for the 59 mg/m^2 to begin.

Regimen Description				
Agent	**Premedication; Precautions**	**Dose And Route**	**Schedule**	**Cycle Length**
Belinostat	See Section 6.4	In 250 mL 0.9% NaCl IV over 30 (±5 min)*** Dose per assigned dose level.	Days 1-5 (week 1)	21 days (3 weeks)
MLN4924 (pevonedistat)	See Section 6.4	In 250 mL D5W or 0.9% NS IV over 60 min (±10 min)* Infusion to start within 60 minutes after belinostat infusion ends. Dose per assigned dose level.	Days 1, 3, & 5 (week 1)**	

IV = Intravenously; D5W = dextrose 5% in water; NS = normal saline.
* May extend or interrupt MLN4924 (pevonedistat) infusion as needed for infusion-related reactions, provided total time from drug reconstitution to end of infusion does not exceed 6 hrs (or within 3 hours of coming to room temperature if previously stored for up to 18 hours as shown in Section 6.1.1).
**Doses of MLN4924 (pevonedistat) must be separated by at least 1 full calendar day. When both drugs are given on the same day (Days 1, 3, 5), start the MLN4924 (pevonedistat) infusion within 60 min after the completion of belinostat infusion.
***May extend belinostat infusion to 3 hrs if infusion-related reactions occur.

6.1.1 MLN4924 (pevonedistat)

MLN4924 (pevonedistat) will be given intravenously 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 if stored at room temperature. Alternatively, the prepared IV bag may be stored for up to 18 hours at 2°C to 8°C (36-46°F). After 18 hours of storage at 2°C to 8°C (36-46°F), the prepared IV bag must be used within 3 hours upon coming to room temperature or must be discarded. When both drugs are given on the same day (Days 1, 3, 5), start the MLN4924 (pevonedistat) infusion within 60 min after the completion of belinostat infusion.

6.1.2 Belinostat

Belinostat will be administered IV over 30 minutes (± 5 minutes) by central or peripheral access through an in-line 0.22-micron filter.

Belinostat infusions may be prolonged up to 3 hrs, if deemed necessary, to ameliorate acute infusion-related reactions (nausea, flushing, rhinitis, vomiting, *etc.*) that may occur during, or immediately following infusion. Once diluted in 250 mL of 0.9% sodium chloride, belinostat may be stored at controlled room temperature (20-25°C) for up to 36 hrs, including the infusion time.

6.2 Definition of Dose-Limiting Toxicity

AEs will be assessed according to the NCI Common Terminology Criteria for Adverse Events

(CTCAE), version 5.0. AEs possibly, probably, or definitely related to study drugs will be scored as toxicities.

All participating sites are expected to notify the Principal Investigator and Study Coordinator within 24 hours of awareness that a DLT has occurred.

- [redacted]

DLTs will be defined in Cycle 1 as any of the following events that are considered by the investigator to be related to therapy with MLN4924 (pevonedistat) and/or belinostat:

- Any grade 3 or greater non-hematological toxicity that does not recover within 1 week to grade ≤1 or baseline with optimal medical management, with the following exception :
  - Grade 3 hypophosphatemia
- Grade 3 or greater ECG QT corrected interval prolonged.
- Grade 3 or greater increased prothrombin time/international normalized ratio (PT/INR) or activated partial thromboplastin time (aPTT) in the absence of anticoagulation therapy.
- Grade 2 or greater elevation of the PT/INR or aPTT that is associated with clinically significant bleeding (CNS, GI, *etc.*).
- Grade 2 or greater increased AST, ALT or bilirubin that persists longer than 2 days between MLN4924 (pevonedistat) doses.
- Delayed initiation of Cycle 2 as follows:
  - More than 2 week delay due to lack of recovery (to < Grade 1 or baseline) from treatment-related non-hematologic toxicity.
  - More than 4 week delay due to lack of recovery (to < Grade 1 or baseline) from treatment-related hematologic toxicity believed not related to leukemic infiltration. Note: Bone marrow evaluation may be required.
- Grade 4 neutropenia or thrombocytopenia extending beyond day 42 in patients with less than 5% blasts in marrow, absence of MDS changes and/or absence of disease by flow cytometry in the marrow.
- Any toxicity that requires discontinuation of either study drug.
- Grade 3 or greater nausea or vomiting despite use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-hydroxytryptamine 3 serotonin receptor antagonist given in standard doses and according to standard schedules.
- Grade 3 or greater diarrhea that occurs despite maximal supportive therapy
- Grade 3 arthralgia or myalgia despite the use of optimal analgesia
- Other grade 2 or greater MLN4924 (pevonedistat)-related non-hematologic toxicities that, in the opinion of the investigator, require a dose reduction or permanent discontinuation of MLN4924 (pevonedistat).

Note that hematologic toxicities are not DLTs except as noted above.

Only DLTs occurring during Cycle 1 will influence decisions regarding dose escalation, expansion of a dose level, or evaluation of intermediate dose levels. Patients will be monitored through all cycles of therapy for treatment-related toxicities.

Patients who for any reason are not evaluable for DLT will be replaced. See Section 9.3.1 for DLT Evaluable Population.

Management and dose modifications for AEs are outlined in Section 7.

6.3 Dose Escalation

Dose escalation will proceed within each cohort according to the following scheme.

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enroll 3 patients at the next dose level.
≥ 2	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 out of 3	Enroll at least 3 more patients at this dose level. If 0 of these 3 patients experience a DLT, proceed to the next dose level (unless MTD has already been exceeded at that dose level, in which case, the current dose level is the MTD). If 1 or more of this group experience DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. Three additional patients will be enrolled at the next lowest dose level if only 3 patients were treated previously at that dose
≤1 out of 6 at highest dose level below the maximally administered dose	This is the MTD and is generally the RP2D. At least 6 patients must be entered at the RP2D.

6.4 Dose Expansion Cohorts

The RP2D may be equal to, but may not exceed, the MTD. A RP2D below the MTD may be considered given the overall tolerability of the treatment including the frequency of AEs that do not qualify as DLTs and the frequency of dose modifications.

Once the RP2D is reached, an additional 12 patients will be treated at this dose. For the expansion cohort, patients will continue to be monitored for occurrence of DLT. If 2 of the first 5

patients or ≥ 2 of 12 patients experience DLT, the principal investigator will discuss with all study investigators and with CTEP whether further addition of patients is needed to re-assess the RP2D. Monitoring of all safety and toxicity data is done by the Principal Investigator and the Corresponding Organization on a real-time basis as data are entered into Medidata Rave using the Web Reporting Module.

6.5 General Concomitant Medication and Supportive Care Guidelines

6.5.1 Information Sheet and Pocket Card

Patients will be given an information sheet on possible interactions with other Agents. Patients will also be given a pocket card identifying the name of the study, study drugs, and contact information. The purpose of this information sheet and pocket card is so that the patient is aware of possible drug interaction risks and can communicate with their regular prescriber(s) and pharmacist. Patients will be encouraged to carry the card with them at all times and to show it to their health care providers so that potential interactions with the study drug can be identified before initiating new medications (Appendix D & Appendix E).

Concomitant Medication Precautions and Exclusions During the Study

Therapy	Comment/Exceptions
CYP450 Isozymes, P-gp, UGT1A1	Concomitant use of any inducers of CYP450 isozymes, any medications that are substrates of CYP2C8 or CYP2C9, any inhibitors of CYP3A/P-gp, or any inhibitors or substrates of UGT1A1 during the study participation is discouraged. If necessitated, such use should prompt treating investigator awareness of possible interactions. and the treating investigator should choose a drug with the least interaction or switch to alternative drugs. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated medical reference.
Acetaminophen and acetaminophen-containing products	Acetaminophen and acetaminophen-containing products should be avoided when possible for 24 hrs before, on the day of, and 24 hrs after dosing with MLN4924 (pevonedistat). When necessary, acetaminophen dose should not exceed 2 grams in a 24 hr period.
Systemic antineoplastic therapy, except for hydroxyurea	Except for hydroxyurea during the first 5 days of Cycle 1, systemic antineoplastic therapies are not permitted. Hydroxyurea dosing may be adjusted to control the level of circulating blast counts. Hydroxyurea dosesmust be recorded.
Anticoagulants	Only anticoagulants that do not affect the aPTT (*e.g.,* warfarin, low molecular heparin and dabigatran) are permitted, unless their use prevents the obtaining of bone marrow samples.

Concomitant Medication Precautions and Exclusions During the Study

Therapy	Comment/Exceptions
BCRP inhibitors	Use of known BCRP inhibitors (*i.e.,* cyclosporine and eltrombopag (Promactal) during the study participation is discouraged. If necessitated, such use should prompt treating investigator awareness of possible interactions. and the treating investigator should choose a drug with the least interaction or switch to alternative drugs.. Because the lists of these agents are constantly changing, it is important to regularly consult a frequently updated medical reference.
Any investigational agent other than MLN4924 (pevonedistat) or belinostat	Other investigational agents are not permitted. For example, androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag (Promacta), or romiplostim (Nplate) are not permitted.
Agents that can cause clinically significant QTc prolongation	To the extent possible, concurrent use of MLN4924 (pevonedistat) and/or belinostat with drugs known to cause clinically significant QT prolongation should be avoided. Such drugs may be identified at the Credible Meds website ([redacted]he Credible Meds website requires free user registration to view the list of clinically relevant QT prolonging drugs, *e.g.,* those known to carry a risk of causing Torsades de Pointes. QT prolonging drugs to be avoided during this trial are shown in the Credible Meds list of "drugs with known TdP risk. When concurrent use of MLN4924 (pevonedistat) or belinostat with any drug on the Credible Meds list of "drugs with known TdP risk" cannot be avoided, review guidance in the "Supportive Care" table prior to concurrent use.

CYP450=cytochrome P450, aPPT=activated partial thromboplastin time.

Concomitant Medications and Procedures Permitted During the Study

Therapy	Comment
Hydroxyurea	Hydroxyurea is allowed for the first 5 days of Cycle 1.
Anti-platelet agents (*e.g.*, aspirin, clopidogrel) and anticoagulants	May be used in patients who have controlled coagulopathy at baseline, as well as those who develop a coagulopathy on study. Note that patients with active uncontrolled coagulopathy are excluded from enrollment.
Myeloid growth factors (*e.g.*, G-CSF, GM-CSF)	In general, the use of myeloid growth factors is discouraged and should be restricted. For patients in CR, CRi, or marrow CR, growth factors may be used in specific circumstances after discussion with the project clinician or designee. Use of growth factors may also be used in patients with grade 3 or grade 4 febrile neutropenia after discussion and agreement with the principal investigator or designee. Additionally, to avoid dose delays, patients who experience grade 4 neutropenia (ANC <500/mcL) with or without fever in Cycle 2 or later may receive granulocyte colony-stimulating factor (G-CSF) or granulocyte macrophage colony-stimulating factor (GM-CSF) between days 28-42 after discussion and agreement with the principal investigator (or designee).
Platelet transfusion	Permitted as medically necessary per institutional guidelines.
Red blood cell transfusion	Permitted as medically necessary per institutional guidelines.

G-CSF=granulocyte colony-stimulating factor, GM-CSF=granulocyte macrophage colony-stimulating factor, CR=complete response, CRi=complete remission with incomplete blood count recovery, ANC=absolute neutrophil count.

Supportive Care Guidelines

Condition	Recommendation
ECG QTc Interval Prolonged	If QTc is ≥450 ms (*i.e.,* grade 1 or higher): • Check potassium and magnesium serum levels. • Correct any identified hypokalemia and/or hypomagnesemia and repeat ECG to confirm QTc. When HR is between 60-100 bpm, manual measurement of QT interval and use of Fridericia calculation is NOT required. When HR <60 or >100 bpm, manual measurement of QT interval by cardiologist is required, with Fridericia correction applied to that manual measurement to determine the QTc. Any questions or concerns about ECG readings will be reviewed with a cardiologist. When concurrent use of MLN4924 (pevonedistat) and/or belinostat with any drug on the Credible Meds list of "drugs with known TdP risk" cannot be avoided, review QTc prior to concurrent use. If pre-concurrent use QTc is: • Grade 0 (<450 ms), follow-up QTc evaluation should be done at the next scheduled visit. • Grade 1 (450-480 ms), follow-up QTc evaluation should be done within 8 days after concurrent use starts. • Grade 2 (481-500 ms), withhold MLN4924 (pevonedistat)/belinostat until follow-up ECG at next possible opportunity shows QTc Grade ≤1 (≤480 ms); evaluate QTc within 8 days after reintroduction of MLN4924 (pevonedistat)/belinostat. Any new onset of dysrhythmia on ECG will be reviewed and managed with input from cardiology. For any episode of syncope (grade 3) pre-syncope (grade 2) or QTc grade 3 or 4 (≥ 501ms or >60 ms change from baseline) or 4 (Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia), see Section 7.
Gastrointestinal Toxicity	Gastrointestinal disturbances, including nausea, vomiting and diarrhea, have been reported with belinostat and may require the use of antiemetic and antidiarrheal medications. Fluid and electrolytes should be replaced to prevent dehydration. Pre-existing nausea, vomiting, and diarrhea should be adequately controlled before beginning therapy.
Antiemetic Therapy	Prophylactic and therapeutic treatment for nausea and vomiting is recommended. The choice of agent is at the discretion of the treating physician. Recommendation to use low-dose dexamethasone, ondansetron (4 mg per dose), or lorazepam. Caution should be exercised when administering ondansetron, palonosetron, or prochlorperazine because of potential QT prolongation risks with belinostat. See above.

Supportive Care Guidelines

Condition	Recommendation
Antidiarrheal Therapy	Diarrhea can occur with belinostat. Study treatment-related diarrhea should be treated with loperamide 4 mg by mouth followed by 2 mg by mouth after each subsequent loose stool up to a maximum of 16 mg daily. Use alternate approaches (such as diphenoxylate-atropine) in patients intolerant of loperamide. Prophylactic loperamide should be considered in patients who have required therapeutic loperamide previously.
Electrolyte Abnormalities	Chemistry tests, including serum electrolytes, creatinine, magnesium, and calcium should be obtained prior to each cycle of therapy. Due to risks of QT prolongation, if hypokalemia and/or hypomagnesemia are present prior to administration of study drug, replete electrolyte(s) before proceeding with treatment. Monitor potassium and magnesium more frequently in symptomatic patients (*e.g.,* patients with nausea, vomiting, diarrhea, fluid imbalance, or cardiac symptoms).
Anemia and Thrombocytopenia	Belinostat can cause thrombocytopenia and anemia. Transfusion of packed RBCs and platelets is recommended per institutional guidelines.
TLS	While TLS is not expected, TLS labs will be performed on Days 1 through 3 of Cycle 1. Additional monitoring, prophylaxis and treatment for TLS is recommended in accordance with published guidelines (Jones *et al.,* 2015). Urinary alkalinization is not recommended.
Anti-infective Prophylaxis	Serious and sometimes fatal infections, including pneumonia and sepsis, have occurred with belinostat. Patients who are or are anticipated to become neutropenic should receive appropriate antimicrobial prophylaxis against bacteria, fungi, and herpes viruses in accordance with published guidelines (Taplitz *et al.,* 2018). Recommendation to use ciprofloxacin 500 mg orally BID. Anti-infective therapies can have potential for QT prolongation and CYP450 interactions.

QTc=Heart-rate corrected QT interval, ECG=Electrocardiogram, RBCs=Red Blood Cells, TLS=Tumor Lysis Syndrome, PTCL=Peripheral T-cell Lymphoma. BID=Twice a day.

6.6 Duration of Therapy

There will be no limitation on the number of cycles administered as long as the patient does not have disease progression or unacceptable toxicity and the study drugs continue to be available. However, patients who attain a CR, CRi, Cytogenetic complete remission (CRc), or molecular complete remission (CRm) and do not go on to have stem cell transplant may discontinue study treatment after 3-4 additional cycles given as "consolidation".

6.7 Discontinuation of Protocol Therapy

Study treatment may continue until one of the following criteria applies:

- Disease progression. Note: Patients with progressive disease may remain on the study, after discussion with principal investigator, if it is judged that they are deriving a clinical benefit from doing so.
- Toxicity requiring that initiation of a new cycle must be delayed >14 days, unless the delay is due to reasons other than toxicity and has been approved by the study principal investigator.
- Toxicity requiring permanent discontinuation of one of the study drugs.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable AEs.
- Achievement of complete remission followed by the administration of 3-4 additional cycles of study treatment as "consolidation".
- Stem cell transplantation.
- 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.
- Patient decides to withdraw from study treatment.
- Determination by the investigator that discontinuation is in the patient's best medical interest.
- Termination of the study by sponsor.
- The drug manufacturer can no longer provide the study agent.
- Patient non-compliance that, in the opinion of the investigator, warrants study treatment discontinuation.
- Patient meets criteria for permanent discontinuation of either study agent.
- Subsequent anti-cancer therapy.

Discontinuation of study treatment does not constitute removal from study. Patients who stop study treatment prematurely transition directly into follow-up per Section 6.6. A patient may be removed from study follow-up and be taken off study for any of the following reasons:

- If in the opinion of the treating physician or principal investigator, it is in the best interest of the patient to do so.
- Patient's decision to discontinue from study follow-up.
- Study sponsor's decision to discontinue the study.

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

6.8 Duration of Follow Up

Patients who go off treatment, regardless of response status, remain in follow-up status for a safety follow-up period of 30 days after the last dose of study agent(s) to capture resolution or stabilization of any ongoing treatment-related AEs, and for capture of any evolving AEs. This safety follow-up period may be truncated if the patient begins any subsequent anticancer therapy that would interfere with assessment of treatment-related AEs during the safety follow-up time period. The safety follow-up period may be extended beyond 30 days if felt necessary to evaluate ongoing treatment-related AEs that have not resolved or stabilized.

After the AE assessment safety follow-up period ends, patients who discontinued treatment with a CR, CRi, CRc, CRm, morphologic leukemia-free state (ML-FS), PR or SD will enter a long-term follow-up period to capture reported clinical status for 2 years or until death, at which time they are taken off study. During this extended follow-up reported clinical status will be monitored by review of clinical documentation or by patient contact approximately every 2 months.

Patients who elect to discontinue follow-up may do so and will be taken off study at that time.

Please refer to Section 11 for the study calendar.

7. DOSING DELAYS/DOSE MODIFICATIONS

7.1 Dose Reduction Steps

Belinostat Dose-Reduction Steps*	**If starting dose of belinostat is:**	
	800 mg/m^2	**1000 mg/m^2**
-1	600 mg/m^2 (Days 1-5)	800 mg/m^2 (Days 1-5)
-2	Discontinue	600 mg/m^2 (Days 1-5)
-3	-	Discontinue
* At the discretion of the investigator, if toxicity has resolved following a required dose reduction, the dose may be escalated, but not to levels higher than the patient's initial dose level and **not during Cycle 1**.		

MLN4924 (pevonedistat) Dose-Reduction Steps*	If starting dose of MLN4924 (pevonedistat) is:					
	15 mg/m²	**20 mg/m²**	**25 mg/m²**	**37 mg/m²**	**50 mg/m²**	**59 mg/m²**
-1	Discontinue	15 mg/m² (Days 1, 3, 5)	20 mg/m² (Days 1, 3, 5)	25 mg/m² (Days 1, 3, 5)	37 mg/m² (Days 1, 3, 5)	50 mg/m² (Days 1, 3, 5)
-2	-	Discontinue	15 mg/m² (Days 1, 3, 5)	20 mg/m² (Days 1, 3, 5)	25 mg/m² (Days 1, 3, 5)	37 mg/m² (Days 1, 3, 5)
-3	-	-	Discontinue	15 mg/m² (Days 1, 3, 5)	20 mg/m² (Days 1, 3, 5)	25 mg/m² (Days 1, 3, 5)
-4	-	-	-	Discontinue	15 mg/m² (Days 1, 3, 5)	20 mg/m² (Days 1, 3, 5)
-5	-	-	-	-	Discontinue	15 mg/m² (Days 1, 3, 5)
-6	-	-	-	-	-	Discontinue

* At the discretion of the investigator, if toxicity has resolved following a required dose reduction, the dose may be escalated, but not to levels higher than the patient's initial dose level and **not during Cycle 1**.

7.2 Dose Modifications

7.2.1 General Guidelines

- AEs will be identified and graded according to the NCI CTCAE v5.0. AEs that are not study drug-related (*e.g.*, disease-related AEs) do not require dose modification. Dose modification for non-study drug-related AEs is generally discouraged but permitted at investigator discretion.
- *Dose Modification for Hematology Toxicities*: There is no dose-modification for hematologic toxicity; however, in cases of non-disease related myelosuppression and when clinically indicated, dose modification will require discussion with PI.
- Dose reduction steps are shown in Section 7.1. Dose modification instructions for both agents are outlined in Section 7.2. Details regarding initiation of new cycles, resumption of treatment within a cycle and dose re-escalation are shown in Sections 7.3, 7.4 and 7.5, respectively.
- Dose modifications (including dose omission, dose reduction, and delays) will be based on the investigator's assessment of the relationship of the toxicity to each of the study drugs.
    - Belinostat should be modified only for AEs thought to be related to belinostat

  - MLN4924 (pevonedistat) should be modified only for AEs thought to be related to MLN4924 (pevonedistat)
  - If the AE could be related to both drugs or if the relationship of the AE is unclear, both study drugs should be modified.
- If a patient experiences several AEs and there are conflicting recommendations for dose modification, the investigator should observe the more cautious modification recommendation. Treatment Delays and Omissions:
  - At the beginning of a cycle:
    - All treatment-related toxicities must be resolved to ≤ grade 1 for initiation of a new cycle (see Section 7.3).
    - Initiation of a new cycle occurs when both agents meet criteria to be given.
    - Delay in initiation of a new cycle by > 14 days requires discontinuation of study therapy.
  - Within a cycle:
    - **On days when only belinostat is due, if treatment criteria aren't met due to toxicity, then the belinostat dose scheduled on that date will be omitted and not made up** on a later date. When belinostat is omitted, patients should be assessed to determine if dosing may resume on the next scheduled dosing day.
    - **On days when both study agents are due, if treatment criteria aren't met due to toxicity, for either agent, then both agents will be delayed**. Dosing days will shift accordingly, allowing delayed treatment to resume on a later date in the cycle - with the exception that no dosing may occur after Day 12 of any cycle. Doses not delivered on or before Day 12 will be omitted for that cycle. When treatment is delayed, patients should be evaluated regularly to determine if dosing may resume, with a goal of delivering as much of the regimen as possible on or before Day 12.
- Permanent discontinuation of either study agent requires discontinuation of study treatment.
- Treatment delay of >14 days requires discontinuation of study treatment.

7.2.2 Non-Hematologic Dose Modifications

Dose modifications, including reductions, omissions and delays, are outlined below for both agents.

Toxicity	Grade (CTCAE v5.0)	Modification of Belinostat [A, B]	Modification of MLN4924 (pevonedistat) [A, B, C]
Nausea Vomiting Diarrhea *(In the absence of optimal medical management; see Section 6.4, Supportive Care Guidelines table)*	2	Continue treatment; no change in belinostat dose.[D]	Continue treatment; no change in MLN4924 (pevonedistat) dose.[D]
	3	• Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due). When toxicity resolves to grade ≤2,[E, F] resume treatment with one dose-reduction step for belinostat.[F] • If grade 3 toxicity recurs following belinostat dose reduction: o Omit belinostat (if only belinostat due); or delay both agents (if both agents due). When toxicity resolves to grade <2[E, F] resume treatment with one dose-reduction step for both drugs.	• Delay both agents until toxicity resolves to grade ≤2.[E, F] Resume treatment with one dose-reduction step for MLN4924 (pevonedistat).[F] • If grade 3 toxicity recurs following MLN4924 (pevonedistat) dose reduction: o Delay both agents until toxicity resolves to grade <2.[E, F] Resume treatment with one dose-reduction step ***for both drugs***.
	4 *(grade 4 NA for nausea)*	• At the investigator's discretion, proceed with one of the following: o Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due). When toxicity resolves to grade <2,[E, F] resume treatment with one dose-reduction step ***for both drugs*** **or** o Discontinue protocol therapy. • If grade 4 toxicity recurs following dose reduction, discontinue protocol therapy	• At the investigator's discretion, proceed with one of the following: o Delay both agents until toxicity resolves to grade <2 E, F Resume treatment with one dose-reduction step for both drugs; or o Discontinue protocol therapy. • If grade 4 toxicity recurs following dose reduction, discontinue protocol therapy

Toxicity	Grade (CTCAE v5.0)	Modification of Belinostat [A, B]	Modification of MLN4924 (pevonedistat) [A, B, C]
Fatigue	2	Continue treatment; no change in belinostat dose.[D]	Continue treatment; no change in MLN4924 (pevonedistat) dose.[D]
	3	• Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due). When toxicity resolves to grade <2,[E, F] resume treatment with one dose-reduction step for belinostat. • If grade 3 toxicity recurs following dose reduction o Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due). When toxicity resolves to grade <2,[E, F] resume treatment with one dose-reduction step ***for both drugs***.	• Delay both agents until toxicity resolves to grade <2.[E, F] Resume treatment with one dose-reduction step for MLN4924 (pevonedistat). • If grade 3 toxicity recurs following dose reduction o Delay both agents until toxicity resolves to grade <2.[E, F] Resume treatment with one dose-reduction step ***for both drugs***.
Increased AST or ALT **Note:** ALT, AST and bilirubin grading will be determined by CTCAE v5.0 in times per ULN irrespective of baseline levels	2	Continue treatment, no change in belinostat dose.[D]	**Occurring on or after Day 3 of a cycle:** delay both agents until toxicity resolves to grade ≤1 or baseline.[E, F] Resume treatment with no change in MLN4924 (pevonedistat) dose.
	3	• Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due). When toxicity resolves to grade <2[E, F] resume treatment with one dose-reduction step for belinostat. • If grade 3 toxicity recurs following dose-reduction of belinostat, discontinue belinostat.	
	4	• Omit belinostat; when toxicity resolves to grade <2,[E, F] resume treatment with one dose-reduction step for belinostat. • If recurrent grade 4 toxicity recurs following belinostat dose reduction, discontinue belinostat.	**Occurring on or after Day 3 of a cycle:** • **OMIT MLN4924 (pevonedistat) for remainder of cycle** (belinostat may continue). • MLN4924 (pevonedistat) may be resumed **in the next cycle at one dose reduction step,** provided the toxicity has recovered to grade ≤1 or baseline.[E, F] Once MLN4924 (pevonedistat) is resumed at reduced dose**, if grade 4 AST or ALT toxicity does not recur** during the cycle given at reduced dose, MLN3924 (pevonedistat) dose may be re-escalated (to no higher than enrollment dose) in a subsequent cycle.

Toxicity	Grade (CTCAE v5.0)	Modification of Belinostat [A, B]	Modification of MLN4924 (pevonedistat) [A, B, C]
Increased Bilirubin	2	• Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due). When toxicity resolves to grade <2,[E, F] resume treatment with one dose-reduction step for belinostat. • If grade 2 or 3 toxicity recurs following belinostat dose reduction, at investigator discretion, omit belinostat; when toxicity resolves to grade <2,[E, F] resume treatment with one dose-reduction step for belinostat.[F]	Occurring on or after Day 3 of a cycle: • Delay both agents until toxicity resolves to ≤1.5 x ULN or baseline.[E, F] Resume treatment with no change in MLN4924 (pevonedistat) dose.
	3		
	4	Discontinue protocol therapy.	Discontinue protocol therapy.

Toxicity	Grade (CTCAE v5.0)	Modification of Belinostat [A, B]	Modification of MLN4924 (pevonedistat) [A, B, C]
Prolonged QTc Interval (*see Section 6.5 for additional information*)	2	• Continue treatment; no change in belinostat dose.[D]	• Continue treatment; no change in MLN4924 (pevonedistat) dose.[D]
	3	• Omit belinostat (if only belinostat due); or delay both agents (if both agents due).E, F • Check and, as indicated, administer potassium to achieve levels ≥4 mmol/L and magnesium to levels ≥2 mg/dL; consider chronic oral supplementation of potassium and/or magnesium. • Review event and attribution with principal investigator prior to patient's next scheduled treatment, considering the following options: o Proceed with belinostat on the same day, if feasible, once QTc ≤480 ms **and** potassium ≥ 4 mmol/L **and** magnesium ≥ 2 mg/dL; or o Omit belinostat (if only belinostat due); or delay both agents (if both agents due) until QTc recovers to ≤480 ms [E,F] • When QTc recovers to ≤480 ms, resume belinostat cautiously, with additional QTc monitoring within 3-8 days from reintroduction. • If QTc prolongation is thought to be related to belinostat, resume treatment with one dose-reduction step for belinostat. • For grade 3 QTc prolongation thought to be related to belinostat that recurs following belinostat dose reduction, discontinue protocol therapy.	• Delay both agents. E, F • Check and immediately administer potassium to achieve levels ≥4 mmol/L and magnesium to levels ≥2 mg/dL; consider chronic oral supplementation of potassium and/or magnesium. • Review event and attribution with principal investigator prior to patient's next scheduled treatment, considering the following options: o Proceed with treatment on the same day, if feasible, once QTc ≤480 ms **and** potassium ≥ 4 mmol/L **and** magnesium ≥ 2 mg/dL; or o Delay both agents until QTc recovers to ≤480ms[E,F] • When QTc recovers to ≤480 ms, resume MLN4924 (pevonedistat) cautiously, with additional QTc monitoring within 3-8 days from reintroduction. • If QTc prolongation is thought to be related to MLN4924 (pevonedistat), resume treatment with one dose-reduction step for MLN4924 (pevonedistat). • For grade 3 QTc prolongation thought to be related to MLN4924 (pevonedistat) that recurs following MLN4924 (pevonedistat) dose reduction, discontinue protocol therapy.
	4	Discontinue protocol therapy.	Discontinue protocol therapy.

Toxicity	Grade (CTCAE v5.0)	Modification of Belinostat [A, B]	Modification of MLN4924 (pevonedistat) [A, B, C]
Pre-Syncope	2	• Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due).[E, F] • Obtain ECG for cardiology review/consultation; IF ECG shows new dysrhythmia or QTc grade ≥2 (>480 ms): o Consider hospitalization for monitoring with cardiology consultation. o Follow instructions above for grade 3 QTc interval. • For recurrent grade 2 pre-syncope or grade 3 syncope thought to be related to belinostat, discontinue protocol therapy.	• Delay both agents.[E, F] • Obtain ECG for cardiology review/consultation; IF ECG shows new dysrhythmia or QTc grade ≥2 (>480 ms): o Consider hospitalization for monitoring with cardiology consultation. o Follow instructions above for grade 3 QTc interval. • For recurrent grade 2 pre-syncope or grade 3 syncope thought to be related to MLN4924 (pevonedistat), consider discontinuation of protocol therapy.
Syncope	3		
Hypophosphatemia	3	• Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due).[E, F] When toxicity resolves to grade ≤1 or tolerable grade 2, resume treatment with one dose-reduction step for belinostat. Note: Hypophosphatemia should be evaluated (including severity and etiology), monitored, and treated according to institutional guidelines.	• Delay both agents.[E, F] • When toxicity resolves to grade ≤1 or tolerable grade 2, resume treatment with one dose-reduction step for MLN4924 (pevonedistat). Note: Hypophosphatemia should be evaluated (including severity and etiology), monitored, and treated according to institutional guidelines.
	4		

Toxicity	Grade (CTCAE v5.0)	Modification of Belinostat [A, B]	Modification of MLN4924 (pevonedistat) [A, B, C]
All Other Non-Hematologic Toxicities[G]	2	Reduce belinostat by one dose-reduction step for any grade 2 toxicity that is intolerable or unresponsive to optimal management.	Reduce MLN4924 (pevonedistat) by one dose-reduction step for any grade 2 toxicity that is intolerable or unresponsive to optimal management.
	3	• Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due). When toxicity resolves to grade ≤1 or tolerable grade 2, [E, F] resume treatment with one dose-reduction step for belinostat. • If grade 3 toxicity recurs following belinostat dose reduction, omit belinostat (if only belinostat due); or delay both agents (if both agents due). When toxicity resolves to grade ≤1 or tolerable grade 2, [E, F] resume treatment with one dose-reduction step ***for both drugs***	• Delay both agents. When toxicity resolves to grade ≤1 or tolerable grade 2,[E, F] resume treatment with one dose-reduction step for MLN4924 (pevonedistat). • If grade 3 toxicity recurs following MLN4924 (pevonedistat) dose reduction, delay both agents. When toxicity resolves to grade ≤1 or tolerable grade 2,[E, F] resume treatment with one dose-reduction step ***for both drugs***
	4	• Omit belinostat (if only belinostat due); **or** delay both agents (if both agents due). When toxicity resolves to grade <2,[E, F] resume treatment with one dose-reduction step ***for both drugs*** • If grade 4 toxicity recurs following dose reduction, discontinue protocol therapy	• Delay both agents. When toxicity resolves to grade <2.,[E, F] resume treatment with one dose-reduction step ***for both drugs*** • If grade 4 toxicity recurs following dose reduction, discontinue protocol therapy

Toxicity	Grade (CTCAE v5.0)	Modification of Belinostat [A, B]	Modification of MLN4924 (pevonedistat) [A, B, C]
Table Footnotes			

A. Refer to the General Guidelines in Section 7.2.1 All treatment related toxicities must be resolved to ≤ grade 1 for initiation of a new cycle (see Section 7.3).
B. On days when only belinostat is due, if treatment criteria aren't met due to toxicity, the belinostat dose scheduled on that date will be omitted and not made up on a later date, with assessment to resume treatment done on the next scheduled dosing day. On days when both study agents are due, if treatment criteria aren't met for both agents, then both agents will be delayed and the schedule shifted to accommodate for the delay. Assessment to resume treatment will be done regularly to determine if dosing may resume, with a goal of delivering as much of the regimen as possible on or before Day 12.
C. For MLN4924 (pevonedistat), a minimum of 1 full calendar day between any 2 doses should be maintained, and a maximum of 3 doses of MLN4924 (pevonedistat) within the cycle must not be exceeded.
D. There are no dose modifications for grade 1 toxicity. For grade 2 toxicity, the dose of the study drug(s) may be reduced by one dose-reduction step at the investigator's discretion.
E. Within a cycle, if treatment is delayed, treatment must be resumed no later than Day 12; and all dosing for a cycle must be completed on or before Day 12.
F. If toxicity has not resolved after 14 days of treatment delay, protocol therapy will be discontinued.
G. Dose modifications are **not** required for asymptomatic laboratory abnormalities (other than increased AST, ALT, and bilirubin, for which dose modifications are listed on the table above).

7.3 Initiation of a New Cycle

See section 7.2 Dose Modifications. Treatment with study drugs will be repeated every 21 days. Initiation of a new cycle requires that all toxicity considered related to treatment with study drugs must have resolved to grade ≤1, to the patient's baseline values, or to a level considered acceptable by the treating physician after discussion with the principal investigator.
If criteria for treatment are not met, initiation of the next cycle of treatment may be delayed for up to 2 weeks. If treatment criteria are not met after a 14-day delay, study treatment will be discontinued.

In certain circumstances and with agreement from the principal investigator, after Cycle 1, consideration may be given to allowing an additional rest week in subsequent cycles thus lengthening the cycle to 4 weeks to support the patient's need for time off between cycles, *e.g.*, during holidays.

7.4 Resumption of Treatment Within a Cycle

See section 7.2 Dose Modifications. MLN4924 (pevonedistat) doses must be separated by at least one full calendar day. In each cycle, a maximum of 3 doses of MLN4924 (pevonedistat) and 5 doses of belinostat should not be exceeded.

7.5 Dose Re-escalation

If a dose reduction is incurred for a ≤ grade 3 toxicity; and that toxicity is resolved ; and that toxicity has not recurred at the reduced dose; then, with approval of the principal investigator (or designee), the dose may be re-escalated (to no higher than the enrollment dose) in the next cycle.

7.6 Dose Modifications Requiring Discontinuation of Protocol Therapy

See section 6.7.

8. PHARMACEUTICAL INFORMATION

A list of the AEs 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(s)

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

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

How Supplied: Takeda supplies and PMB distributes MLN4924 (Pevonedistat HCl) formulated as 10 mg/mL Concentrate for Solution for Infusion. Each single-use vial contains either 50 mg (5 mL) or 44 mg (4.4 mL) free base equivalent containing the following excipients: citric acid (anhydrous), trisodium citrate dihydrate, and Betadex Sulfobutyl Ether Sodium (Captisol®) at pH 3.3. 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 (15°-30°C/59°-86°F) for 15 minutes. Do not use a water bath to warm up the vials. Return vials to 2°-8°C (36°-46°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 o Final volume (250 mL) = Drug + D5W or NS
  - Do not shake; gently mix the IV solution by inverting the IV bag several times
  - Inspect the IV solution to ensure it is clear and free of visible particles

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

Storage: Store MLN4924 (Pevonedistat HCl) refrigerated at 2°-8°C (36°-46°F) in its original

carton to protect from light.

If a storage temperature excursion is identified, promptly return MLN4924 (Pevonedistat HCl) to 2°-8°C (36°-46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to [redacted] determination of suitability.

Stability: Stability studies 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 2^0-8^0C (36^0-46^0F), after which the IV bag can be used within 3 hours upon removal from 2^0-8^0C 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 peripheral IV-line, midline or central venous access. The IV infusion can be slowed or stopped and restarted for any associated infusion-related reactions. The total time from the IV preparation to end of IV infusion must not exceed 6 hours. Infusion line can be flushed with 5% Dextrose in Water or 0.9% Normal Saline 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. Therefore, drugs that are CYP3A/P-gp inhibitors can be used in patients receiving MLN4924 (pevonedistat).

In vitro, pevonedistat is not an inhibitor of CYP1A2, 2C9, 2C19, 2D6, or 3A4/5 (IC50 > 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.

Because the metabolic and excretion pathways of pevonedistat remain to be fully characterized in

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

8.1.2 Belinostat (NSC # 726630)

Chemical Name: (E)-N-hydroxy-3-(3-(N-phenylsulfamoyl)phenyl)acrylamide

Other Names: PXD101; Beleodaq®

Classification: HDAC inhibitor

CAS Registry Number: 414864-00-9; 866323-14-0

Molecular Formula: $C_{15}H_{14}N_2O_4S$ **M.W.**: 318.35

Approximate Solubility: Water 0.14 mg/mL; ethanol >200 mg/mL;

polyethylene glycol 400 ~ 1.5 mg/mL; 1,2-propanediol ~ 0.2 mg/mL

Mode of Action: Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones. Belinostat is a novel and potent HDAC inhibitor of the hydroxamate class. It alters acetylation levels of histone and non-histone proteins, thus influencing chromatin accessibility and ultimately gene transcription.

How Supplied: Spectrum Pharmaceuticals supplies and the PMB, CTEP, DCTD distributes belinostat in single-use 30 mL clear glass vials with coated stoppers and aluminum crimp seals with "flip-off" caps containing 500 mg belinostat for injection. The sterile yellow lyophilized product also contains 1000 mg arginine, European Pharmacopoeia/ US Pharmacopoeia (Ph. Eur/USP).

Preparation: Reconstitute the lyophilized product with 9 mL sterile water for injection to yield a final belinostat concentration of 50 mg/mL. Before IV administration, further dilute in 250 mL 0.9 % sodium chloride injection.

Storage: Store intact vials of belinostat at controlled room temperature (20-25°C; 68-77°F); brief excursions permitted (15-30°C; 59-86°F). Leave intact vials of belinostat in the secondary packaging until use.

If a storage temperature excursion is identified, promptly return belinostat to controlled room temperature and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to [redacted] for determination of suitability.

Stability: Shelf life stability studies of intact vials of belinostat are on-going; once the lyophilized product is reconstituted, the vialed solution is stable for up to 12 hours at ambient temperature (15-25°C).

Once further diluted in 250 mL of 0.9% sodium chloride, belinostat may be stored at ambient temperature (15-25°C) for up to 36 hours, including the infusion time.

Route and Method of Administration: Infuse belinostat IV over 30 minutes through a 0.22

micron in-line filter.

Potential Drug Interactions*:* Belinostat is primarily metabolized by hepatic UGT1A1, and to a lesser extent by CYP2A6, CYP2C9 and CYP3A4 enzymes. Avoid concomitant use of strong inhibitors of UGT1A1. Use caution when co-administering agents which may compete for UGT1A1 metabolism, such as irinotecan. Patients with known UGT1A1 genetic polymorphisms, such as UGT1A1*28, can have reduced UGTA1A activity and may be at risk for increased belinostat exposure. If subjects with UGT1A1 genetic polymorphisms are not excluded from study participation, reduced doses are warranted.

In vitro studies have shown belinostat and its metabolites are weak to moderate inhibitors of CYP2C8 and moderate to strong inhibitors of CYP2C9; however, studies did not demonstrate effects when co-administered with warfarin. Avoid CYP2C8 and CYP2C9 substrates during belinostat treatment unless deemed medically necessary.

Belinostat is likely a P-gp substrate but is unlikely to inhibit P-gp.

Avoid concomitant medications that may cause Torsade de Pointes.

Availability: Belinostat is an investigational agent supplied to investigators by the DCTD, NCI. Belinostat is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Section 13).

8.1.3 Agent Ordering and Agent Accountability

8.1.3.1 NCI-supplied agents

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.

8.1.3.2 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.

8.1.4 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.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design/Endpoints

This study will be a phase 1 trial of MLN4924 (pevonedistat) and belinostat in relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome employing a "3+3" dose escalation strategy applied to 4 dose levels, with provision for 1 level of dose reduction. Additional patients will be enrolled at the MTD until a total of 12 patients have been treated at the MTD.

Primary endpoint

- RP2D for the combination of MLN4924 (pevonedistat) and belinostat in the study population.

Secondary endpoints

- AEs using NCI CTCAE v5.0.

- Treatment responses classified according to International Working Group (IWG) and European Leukemia Net (ELN) criteria for response assessment in AML and MDS. Duration of response defined as the time from documentation of tumor response to disease progression or death, whichever occurs first. Time to response defined as the time from registration to the time of documentation of tumor response.
- [redacted]
- MLN4924 (pevonedistat) and belinostat plasma concentrations measured at baseline (pre-treatment) and at defined time points in Cycle 1.
- Candidate biomarker levels in bone marrow and/or blood samples pre- and 24-hr post-treatment with the first doses of study drugs (*e.g.,* p-Wee1, p-cdc2 and γ-H2A.X).

9.2 Sample Size/Accrual Rate

With this classical 3+3 design, there is no statistical testing, rather a variety of dose-escalation strategies will be employed to target a DLT rate of <33%. Applying this design to the 5 dose levels (-1, 1, 2, 3 and 4), starting with dose level 1 (as indicated in Table 1 in Section 6), the total number of patients evaluable for DLT ranges from 3 to 24. Assuming an average of 4 or 5 patients per dose level (some may require 3, other 6), approximately 18 patients can be anticipated. Accounting for approximately 20% of patients subsequently found to not be evaluable for DLT, enrollment of 23 patients is expected in Part A (3+3 phase), with a maximum of 30.

During the expansion cohort for dose/schedule refinement (Iasonos and O'Quigley, 2016), an additional 15 patients (factoring in the 20% DLT inevaluability as well) will be treated at MTD, leading to a maximum sample size of 45, with a likely size between 35-42

Stopping rule: The 3+3 is a straightforward algorithmic design, where development of DLTs in more than 1 of 6 subjects in a specific dose cohort suggests that the MTD has been exceeded, and further dose escalation is not pursued. So here, the stopping rule is to repeat until MTD is achieved, or the trial is stopped.

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	7	6	0	0	**13**

Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
White	16	14	1	1	**32**
More Than One Race	0	0	0	0	**0**
Total	**23**	**20**	**1**	**1**	**45**

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9.3 Evaluability for DLT, Toxicity, and Response

9.3.1 DLT-Evaluable Population

Each registered patient will be deemed as evaluable for DLT if the patient has received sufficient exposure to the prescribed study treatment and has been observed for the required duration (the DLT-evaluation period), or has experienced a DLT once initiating the study treatment. To meet criteria for sufficient exposure, a patient must have received during the DLT-evaluation period (*i.e.,* Cycle 1):

- at least 4 of 5 planned doses of belinostat; and
- at least 2 of 3 planned doses of MLN4924 (pevonedistat)

Patients who for any reason are not evaluable for DLT will be replaced.

9.3.2 Safety-Evaluable Population

Each registered patient will be deemed evaluable for toxicity (AE evaluation) if the patient has received any study treatment.

9.3.3 Response-Evaluable Population

Response-evaluable patients are those who have received any doses of belinostat or MLN4924 (pevonedistat) and have had at least one post-treatment response evaluation. For response evaluation, the patients are coded as having a response or not having a response as follows:

- Responders - Those patients whose best response assessment is a CR, CRi, CRc, CRm, ML-FS, or PR.
- Non-Responders - Those patients whose best response assessment is SD, morphologic relapse, or progression, or those patients who were not assessed or who were not evaluable.

The coding of patients as responders or non-responders will be made by the PI with the concurrence of the biostatistician.

9.4 Statistical Analysis

All statistical analyses will be descriptive in nature for this phase 1 study.

9.4.1 Statistical Analysis for Primary Objective

Patients' treatment dosing level, dose modification, DLTs, and evaluability for DLTs will be listed and summarized by basic descriptive statistics (such as frequency and proportion). The RP2D will be found based on the criteria defined in Section 6.

9.4.2 Statistical Analyses for Secondary Objectives

Toxicities: AEs and SAEs, dosing levels, treatment received, best clinical response, and demographics will be listed. Basic descriptive statistics will be used to summarize toxicities related to the study drugs by grade, and all toxicities, whether related or unrelated to the study drugs.

Anti-tumor activity: For the response rate calculations, all study reports will contain at least a section with all enrolled patients. Other sections of the reports may detail the response rate for response-evaluable patients only. All response rate analyses based on a subset of patients will be accompanied by explanations of which patients were excluded and the reasons; 95% confidence limits will be given. For patients who do not have disease progression or have not died at time of analysis, the last date the patient was known to be alive and progression free will be used for duration of response analysis. If there are at least 3 responses, duration of response and time to response will be summarized by the first, second, and third quantiles and illustrated by a Kaplan-Meier plot.

[redacted]

PK interactions: PK parameters in MLN4924 (pevonedistat) and in belinostat will be calculated using standard non-compartmental methods and summarized as geometric mean and geometric coefficient of variation. C_{max} and the times needed to reach these concentrations (t_{max}) will be assessed by inspection of the concentration versus time plots. The AUC will be calculated from time zero to infinity ($AUC_{0-\infty}$). V_d and $t_{1/2}$ will also be calculated accordingly. To discover any potential PK interactions between the 2 agents, each PK parameter will be compared with each referenced PK parameter for those who receive single-agent at the same amount dose by a one-sample t-test. The normality of the PK parameters will be checked, and data transformation may be performed if data are highly skewed.

[redacted]

[redacted]

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

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 (Section 10.2) will determine whether the event requires expedited reporting (Section 10.3) via the CTEP Adverse Event Reporting System (CTEP-AERS) **in addition** to routine reporting (Section 10.4).

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 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 [redacted] 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 CAEPRs for CTEP IND Agents

10.1.1.1 CAEPR for MLN4924 (pevonedistat)

Frequency is provided based on 474 patients. Below is the CAEPR for MLN4924 (pevonedistat) HCl.

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		

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%)**	
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		***Muscle cramp (Gr 2)***
Myalgia			***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
	Nervous system disorders - Other (neuropathy peripheral, peripheral neuropathy)		
	Paresthesia		
PSYCHIATRIC DISORDERS			
	Anxiety		
	Confusion		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	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 [redacted] 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.

10.1.1.2 CAEPR for Belinostat

Frequency is provided based on 583 patients. Below is the CAEPR for Belinostat (PXD-101, NSC 726630).

Version 2.7, October 29, 2018[1]

Adverse Events with Possible Relationship to Belinostat (PXD-101) (CTCAE 5.0 Term) [n= 583]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2] (Gr 3)***
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Aspartate aminotransferase increased		
	Creatinine increased		
	Electrocardiogram QT corrected interval prolonged		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
		Tumor lysis syndrome	
NERVOUS SYSTEM DISORDERS			
	Dizziness		

Adverse Events with Possible Relationship to Belinostat (PXD-101) (CTCAE 5.0 Term) [n= 583]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Dysgeusia		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		***Dyspnea (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
	Flushing		***Flushing (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 P[redacted] Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on Belinostat (PXD-101) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Belinostat (PXD-101) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Atrial fibrillation; Cardiac disorders - Other (bundle branch block left); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular fibrillation
EYE DISORDERS - Eye disorders - Other (visual loss); Vision decreased
GASTROINTESTINAL DISORDERS - Abdominal distension; Dyspepsia; Gastroesophageal reflux disease; Mucositis oral; Rectal hemorrhage; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Flu like symptoms; General disorders and administration site conditions - Other (general physical health deterioration); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatic cirrhosis)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Infusion related reaction; Tracheal hemorrhage
INVESTIGATIONS - Alkaline phosphatase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Cholesterol high; Ejection fraction decreased; Electrocardiogram T wave abnormal; INR increased; Investigations - Other (prothrombin time shortened); Investigations - Other (total protein decrease); Lipase increased; Weight gain
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia;

Hypermagnesemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Dysesthesia; Encephalopathy; Lethargy; Nervous system disorders - Other (apraxia); Nervous system disorders - Other (burning sensation); Peripheral sensory neuropathy; Reversible posterior leukoencephalopathy syndrome; Seizure; Stroke; Syncope
PSYCHIATRIC DISORDERS - Confusion; Depression; Insomnia; Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (azotemia); Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema; Vaginal inflammation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Hiccups; Hypoxia; Nasal congestion; Pneumonitis; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus; Urticaria
VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Phlebitis; Thromboembolic event; Vasculitis

Note: Belinostat (PXD-101) 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.

10.2 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 [redacted]

- **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.
    - Other Aes for the protocol that do not require expedited reporting are outlined in Section 10.3.4.

- **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 [redacted]

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 both 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 **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI 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

10.3.4 Additional Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, the AEs/grades listed below do not require expedited reporting via CTEP-AERS. However, they still must be reported through the routine reporting mechanism regardless of attribution (Section 10.4). The listed AEs are excluded from expedited reporting ***regardless of*** whether they result in ≥24 h hospitalization of a patient.

CTCAE SOC	Adverse Event	Grade
Blood and lymphatic system disorders	Febrile neutropenia	3
	Anemia	3 or 4
	Leukocytosis	3 or 4
Investigations	White blood cell count decreased	3 or 4
	Lymphocyte count decreased	3 or 4
	Neutrophil count decreased	3 or 4
	Platelet count decreased	3 or 4

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" [redacted] 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.*, 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

Unless stated otherwise, baseline evaluations are to be conducted within 1 week prior to start of protocol therapy. Bone marrow evaluations for disease assessment must be done ≤ 3 weeks prior to start of therapy. Scans and X-rays must be done ≤2 weeks prior to the start of therapy. Hepatitis serologies and left ventricular ejection fraction assessment should be done ≤4 weeks prior to the start of therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hrs prior to initiation of the next cycle of therapy.

Study Calendar

	Baseline[a,b,t]	Cycle 1							Subsequent Cycles							End of Treatment[c]	End of 30-Day Safety Follow-up[d]	Extended Follow-up[d,e]
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15			
MLN4924 (pevonedistat)		A		A		A			A		A		A					
Belinostat		B	B	B	B	B			B	B	B	B	B					
Performance status	X																	
LVEF assessment by echocardiogram or radionuclide angiography	X[r]																	
History and physical exam and weight.	X	X[a]							X[a]							X		
Urinalysis [f]	X																	
Informed consent	X																	
Vital signs (T, P, R, BP, pulse oximetry)	X	X		X		X			X		X		X			X		
Height	X																	
Demographics	X																	
Concurrent medications[g]	X	X[a]							X[a]							X		
Baseline symptoms and conditions	X																	
AE assessment		X----------													----------X	X	X	
CBC, differential, platelet count	X	X		X		X	X	X	X[a]							X		
Basic metabolic panel[h], eGFR	X	X	X	X		X	X	X	X[a]		X[a]		X[a]			X		
Uric acid, Mg^{2+}	X	X	X	X			X	X	X[a]							X		
PT/INR, PTT	X	X					X	X	X[a]									
Hepatic panel[i,j]	X	X		X		X	X	X	X[a]		X[a]		X[a]			X		
LDH, PO_4	X	X	X	X														
CD4; HIV viral load[u]	X																	
Hepatitis serologies (Hep B SAg, Hep B S Ab, Hep B c Ab;Hep B viral load)[k, v]	X																	

	Baseline[a,b,t]	Cycle 1							Subsequent Cycles							End of Treatment[c]	End of 30-Day Safety Follow-up[d]	Extended Follow-up[d,e]
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15			
Hepatitis C viral load[v]	X																	
ECG	X				X[l]													
Serum or urine pregnancy test	X	X[a, m]							X[a,m]									
Disease assessment[n, s]	X[s]	Every two cycles																
Reported clinical status																		X
Blood for PK studies		X[o]																
Blood or bone marrow aspirate for PD studies[p]	X	X																
[redacted]	[redacted]																	

A. MLN4924 (pevonedistat): Dose as assigned; IV over 60 minutes (± 10 minutes) once daily (QD) on Days 1, 3, and 5 of each 21-day cycle. When both drugs are given on the same day (Days 1, 3, 5), start the MLN4924 (pevonedistat) infusion within 60 mins after the completion of belinostat infusion.
B. Belinostat: Dose as assigned; IV over 30 minutes QD on Days 1-5 of each 21-day cycle. Infusion may be extended to 3 hours pending patient tolerance.
a. Prior to treatment
b. Unless stated otherwise, baseline evaluations are to be conducted within 1 week prior to start of study therapy. Repeat if not within 1 week prior to Cycle 1, Day 1. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hrs prior to initiation of the next cycle of therapy.
c. End of treatment visit occurs after completion of all study treatment.
d. See Section 6.8.
e. Only for patients with a CR, CRi, CRc, CRm, ML-FS, PR, or SD, capture reported clinical status approximately every 2 months for 2 years following end of safety follow-up until disease progression or death. See Section 6.8.
f. Urinalysis to include turbidity and color, pH, specific gravity, protein, ketones, bilirubin, occult blood, nitrite, glucose, and leukocyte esterase. Microscopic analysis should be done at the discretion of the treating physician.
g. Include over-the-counter medications.
h. Sodium, potassium, carbon dioxide content, chloride, creatinine, blood urea nitrogen (BUN), glucose and calcium.
i. Alkaline phosphatase, ALT, AST and total bilirubin assessments must be performed and read prior to each dose of MLN4924 (pevonedistat).
j. Total bilirubin, direct bilirubin, ALP (alkaline phosphatase), AST, ALT, total protein, albumin.
k. Hepatitis serologies and, if needed, HBV viral load testing are to be done ≤4 weeks prior to the start of therapy. HBV viral load only necessary if patients are Hepatitis B Ab positive.
l. Pre- & post-treatment on Cycle 1 Day 4 and whenever clinically indicated. Patients with risk factors for QT prolongation including CHF, bradyarrythmias, electrolyte abnormalities or those on other drugs known to prolong the QT/QTc interval, such as Class Ia and III anti-arrhythmics, should be closely monitored as clinically indicated with ECGs and serum electrolytes (magnesium, potassium) while on study treatment. See Section 6.5.
m. For women capable of pregnancy: pregnancy test within 7 days prior to start of treatment. In addition, review pregnancy risks and offer pregnancy test as clinically indicated.

	Baseline[a,b,t]	Cycle 1							Subsequent Cycles							End of Treatment[c]	End of 30-Day Safety Follow-up[d]	Extended Follow-up[d,e]
		Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 15			

n. Baseline/pre-treatment bone marrow procedure may be done within 3 weeks prior to start of therapy. For patients with AML, baseline assessments should also include NPM1, FLT3, and CEBPA. If these markers cannot be assessed at study baseline, markers from bone marrow assessment done at any time point prior to study baseline may be reported.
o. For PK samples time points, see Section 5.3.3. Note: when feasible, Cycle 1, Day 1 treatment should be started in the morning to allow for the timing of PK collections. If unforeseen delays occur sample collections may be missed
p. For pharmacodynamic samples, see Sections 5.3 and 5.4
q. For PG samples: see Section 5.4
r. LVEF assessment should be done $\leq$4 weeks prior to the start of therapy.
s. Scans or x-ray for disease assessment should be done $\leq$ 2 weeks prior to start of therapy.
t. Unless stated otherwise, baseline evaluations are to be done within 1 week prior to start of therapy.
u. HIV testing not required for eligibility. Persons with known HIV-positivity must have CD4 and HIV viral load testing $\leq$4 weeks prior to the start of therapy.
v. Hepatitis C testing not required for eligibility. Persons with history of Hepatitis C virus infection must have HCV viral load testing. testing $\leq$4 weeks prior to the start of therapy.

12. MEASUREMENT OF EFFECT

Although the clinical benefit of these drugs has not yet been established, the intent of offering this treatment is to provide a possible therapeutic benefit, and thus the patient will be carefully monitored for tumor response and symptom relief in addition to safety and tolerability. Patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be re-evaluated at the end of every even cycle. Additional bone marrow procedures may also be obtained as clinically indicated following initial documentation of a CR.

12.1 Hematologic Tumors

Treatment responses will be classified according to the IWG revised criteria for response assessment in AML (Cheson *et al*., 2003); the ELN recommendations for diagnosis and management of AML (Dohner *et al*., 2010); and the IWG application and proposal for modification of response criteria in MDS (Cheson *et al*., 2006).

Bone marrow blast percentages will be defined by manual differential count on the aspirate.

Morphologic complete remission (CR): <5% bone marrow blasts and no blasts with Auer rods with no requirement for bone marrow cellularity, as long as absolute neutrophil count (ANC) ≥1000/mcL AND platelets ≥100,000/mcL, patient is transfusion-independent, and has no residual evidence of extramedullary leukemia. Persistent dysplasia is allowed.

Morphologic complete remission with incomplete blood count recovery (CRi): All criteria for morphologic CR must be met, except that the patient has residual neutropenia (ANC <1000/mcL) or thrombocytopenia (platelets <100,000/mcL).

Morphologic leukemia-free state (MLPS): <5% bone marrow blasts, no blasts with Auer rods, and no persistent extramedullary leukemia, peripheral blood count recovery not required.

Cytogenetic complete remission (CRc): There should be no evidence of a previously present cytogenetic abnormality (*e.g.,* t(8;21), inv 16, t(9;22), *etc*.) by conventional karyotyping or Fluorescent in situ hybridization (FISH) (must be specified).

Molecular complete remission (CRm): There should be no evidence of a previously present molecular abnormality (*e.g.,* BCR-ABL, mutated FLT3, NPM1, or CEBPA, *etc.*). The sensitivity of the PCR assay must be specified.

Partial remission (PR): All peripheral blood criteria for CR must be met, with a decrease of at least 50% in the percentage of blasts to 5% to 24% in the bone marrow aspirate. A value of <5% bone marrow blasts will be considered a PR if Auer rods are present.

Stable disease (SD): Patients not meeting criteria for CR, CRi, ML-FS, CRc, CRm, PR, relapse, or progressive disease.

Morphologic relapse: Relapse after CR is defined as reappearance of leukemic blasts in the

peripheral blood or ≥5% blasts in the bone marrow not attributable to any other cause (*e.g.,* bone marrow regeneration). Relapse from PR is defined as ≥25% bone marrow blasts not attributable to bone marrow regeneration or use of colony stimulating factors. The appearance of new dysplastic changes should also be considered relapse.

Progressive Disease: Any of the following in patients who have not previously met CR, CRi, CRc, CRm, ML-FS, or PR criteria while on study therapy:

- ≥50% increase in the bone marrow blasts (by aspirate differential count) over the best previous assessment (comparing to a minimum bone marrow blast percentage threshold of 20% at baseline or during study at such time as that threshold is met).
- ≥50% increase in peripheral blood absolute blast count over the best previous assessment (comparing to a minimum peripheral blood absolute blast count threshold of ≥1000/mcL at baseline or during study at such time as that threshold is met). In some cases, the peripheral blood absolute blast count may not accurately reflect disease burden, especially with targeted therapies. At investigator discretion, the patient can continue on study with close monitoring of peripheral blood absolute blast count and bone marrow biopsies to assess bone marrow blast percentage (by aspirate differential count) as clinically indicated.
- Development of new extramedullary disease.

Appearance of new dysplastic changes should be closely monitored for emerging relapse. In a patient who has been recently treated, dysplasia or a transient increase in blasts may reflect a chemotherapy effect and recovery of hematopoiesis. Cytogenetics should be tested to distinguish true relapse from therapy-related MDS/AML.

Duration of remission is defined only for patients who achieve CR, CRi, CRc, or CRm and is measured by the interval from the date of CR (by blood count recovery and BM examination), until the date of relapse.

Cytogenetic responses: For patients with AML or MDS, a complete cytogenetic response requires the disappearance of a previously present cytogenetic abnormality (without appearance of new ones), while a partial cytogenetic response requires a ≥50% reduction in the number of metaphases positive for the chromosomal abnormality by conventional karyotyping.

13. STUDY OVERSIGHT AND DATA REPORTING / REGULATORY REQUIREMENTS

AE 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

SAEs; reporting of expedited AEs; and accumulation of reported adverse events from other trials testing the same drug(s). The Protocol Principal Investigator and statistician have access to the data at all times through the CTMS web-based reporting portal.

For the phase 1 portion of this study, all decisions regarding dose escalation/expansion/de-escalation require sign-off by the Protocol Principal Investigator through the CTMS/IWRS. In addition, for the Phase 1 portion, the Protocol Principal Investigator will have at least monthly, or more frequently, conference calls with the Study Investigators and the CTEP Medical Officer(s) to review accrual, progress, and adverse events and unanticipated problems.

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.
Requirements to access Rave via iMedidata:

- A valid account, and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
  Rave role requirements:
    - Rave CRA or Rave CRA (Lab Admin) role, must have a minimum of an Associate Plus (AP) registration type,
    - Rave Investigator role, must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR), and
    - Rave Read Only role, site staff must have at a minimum an Associates (A) registration type.
- [redacted] for registration types and documentation required.

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 [redacted]g 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 receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the [redacted]

13.2.1 Method

This study will be monitored by the 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 [redacted]

13.2.2 Responsibility for Data Submission

For ETCTN trials, it is the responsibility of the Principal Investigator(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 [redacted] and

CTSU websites.

[redacted] Customized eCRFs will be included when appropriate to meet unique study requirements. The Principal Investigator 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 [redacted]

[redacted] 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 CTEP Multicenter Guidelines

N/A

13.5 DLT Reports

All DLT events are reported to the Principal Investigator and study coordinator within 1 working day by email or fax ([redacted]

13.6 Safety Updates

The North American Star Consortium (NASC) Corresponding Organization is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

13.7 Real Time Summary and Communication from Coordinating Study Team to Participating Sites

On the basis of DLT reports and data reports, the coordinating study team will maintain a real-time summary of study progress to date including patients enrolled by dose level and DLT events. On the basis of the real-time summary, information important to patient safety is communicated from the coordinating study team to participating sites by monthly teleconferences and on an as needed basis by email.

13.8 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 (cooperative research and development 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" [redacted] 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: [redacted]

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 ([redacted]). 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 Principal Investigator 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:

[redacted]

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

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APPENDIX 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 hrs.	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 hrs.	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 NEW YORK HEART ASSOCIATION CLASSIFICATION OF HEART FAILURE.

New York Heart Association Classification of Heart Failure	
Class I	No symptoms. Ordinary physical activity such as walking and climbing stairs does not cause fatigue or dyspnea.
Class II	Symptoms with ordinary physical activity. Walking or climbing stairs rapidly, walking uphill, walking or stair climbing after meals, in cold weather, in wind or when under emotional stress causes undue fatigue or dyspnea.
Class III	Symptoms with less than ordinary physical activity. Walking one to two blocks on the level and climbing more than one flight of stairs in normal conditions causes undue fatigue or dyspnea.
Class IV	Symptoms at rest. Inability to carry on any physical activity without fatigue or dyspnea.

APPENDIX C: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **MLN4924 (Pevonedistat)**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

MLN4924 interacts with certain specific enzyme in your liver, and certain transport proteins that help move drugs in and out of cells.

- The enzymes in question are CYP3A4/5. MLN4924 is broken down by CYP3A4/5 and may be affected by drugs that are moderate or strong inducers of CYP3A4/5.
- The transporter enzymes and proteins in question are P-glycoprotein (P-gp). OATP and BCRP. MLN4924 is moved in and out of cells/organs by P-gp, and BCRP. Use caution with concomitant drugs that are inhibitors of P-gp . MLN4924 may affect the ability of other drugs to be moved in and out of cells by inhibiting P-gp, OATP and BCRP. Use substrates of these transport proteins with caution.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

MLN4924 may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

MLN4924 must be used very carefully with other medicines that use certain liver enzymes or transport proteins to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered moderate or strong inhibitors or inducers of CYP3A4/5, P-gp, OATP and BCRP.

- Please be very careful! Over-the-counter drugs (including herbal supplements) may contain ingredients that could interact with your study drug. Speak to your doctors or pharmacist to determine if there could be any side effects.
- 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. Your study doctor's name is _____ and he or she can be contacted at _____.

(08/18)

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **MLN4924.** This clinical trial is sponsored by the NCI. **MLN4924** may interact with drugs that are processed by your liver, or use certain transport proteins in your body. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement (e.g., St. John's Wort)

MLN4924 interacts with a specific liver enzyme called CYP3A4/5 and transport proteins called P-gp, OATP and BCRP and must be used very carefully with other medicines that interact with these enzymes and transport proteins.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered "strong inhibitors/inducers of CYP3A4/5, P-gp, and OATP
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.

APPENDIX E: PATIENT DRUG INFORMATION HANDOUT AND WALLET CARD

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

The patient _____ is enrolled on a clinical trial using the experimental study drug, **Belinostat**. This clinical trial is sponsored by the National Cancer Institute. This form is addressed to the patient but includes important information for others who care for this patient.

These are the things that you as a healthcare provider need to know:

- Belinostat has potential drug interactions of concern
    - Drugs that may cause Torsade de Pointes should be avoided.
    - Belinostat is broken down in the liver mostly by UTG1A1, and, to a lesser extent, by CYP2A6, CYP2C9 and CYP3A4 enzymes.
        - Strong inhibitors of UGT1A1 **should be avoided**.
        - Drugs that compete for UGT1A1 for metabolism, such as irinotecan, should be used with caution.
        - Patients with known UGT1A1 genetic polymorphisms, such as UGT1A1*28, can have reduced UGT1A1 activity, placing them at risk for belinostat overexposure.
        - CYP2C8 and CYP2C9 substrates should be avoided during treatment with belinostat unless deemed medically necessary.
    - Belinostat is likely a substrate of the transporter enzymes and proteins P-glycoprotein (P-gp) but is unlikely to inhibit P-gp. There are no specific interactions of concern based on P-gp.

To the patient: Take this paper with you to your medical appointments and keep the attached information card in your wallet.

Belinostat may interact with other drugs which can cause side effects. For this reason, it is very important to tell your study doctors of any medicines you are taking before you enroll onto this clinical trial. It is also very important to tell your doctors if you stop taking any regular medicines, or if you start taking a new medicine while you take part in this study. When you talk about your current medications with your doctors, include medicine you buy without a prescription (over-the-counter remedy), or any herbal supplements such as St. John's Wort. It is helpful to bring your medication bottles or an updated medication list with you.

Many health care providers can write prescriptions. You must tell all your health care providers (doctors, physician assistants, nurse practitioners, pharmacists) you are taking part in a clinical trial.

These are the things that you and they need to know:

Drugs known to cause Torsade de Pointes should be avoided.

Belinostat must be used very carefully with other medicines that use certain liver enzymes to be effective or to be cleared from your system. Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered strong inhibitors of UGT1A1 or substrates of CYP2C8 and CYP2C9.

- 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.

- 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.

Your study doctor's name is _____ and he or she can be contacted at _____.

STUDY DRUG INFORMATION WALLET CARD

You are enrolled on a clinical trial using the experimental study drug **Belinostat.** This clinical trial is sponsored by the NCI. **Belinostat** may interact with drugs that are processed by your liver or that can cause a condition of the heart known as Torsade de Pointes. Because of this, it is very important to:

- Tell your doctors if you stop taking any medicines or if you start taking any new medicines.
- Tell all your health care providers (doctors, physician assistants, nurse practitioners, or pharmacists) that you are taking part in a clinical trial.
- Check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement (e.g., St. John's Wort)

Belinostat interacts with liver enzyme called UGT1A1, CYP2C8 and CYP2C9 and must be used very carefully with other medicines that interact with these enzymes and transport proteins.

Belinostat should not be used at the same time with drugs that can cause Torsade de Pointes.

- Before you enroll onto the clinical trial, your study doctor will work with your regular health care providers to review any medicines and herbal supplements that are considered
  - strong inhibitors of UTG1A1 or
  - substrates of CYP2C8 or CYP2C9 or
  - drugs that can cause Torsade de Pointes
- Before prescribing new medicines, your regular health care providers should go to a frequently-updated medical reference for a list of drugs to avoid, or contact your study doctor.
- Your study doctor's name is _____

  and can be contacted at _____.