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CHILDREN'S ONCOLOGY GROUP

ADVL1615

A PHASE 1 STUDY OF PEVONEDISTAT (MLN4924, [redacted]), A NEDD8 ACTIVATING ENZYME (NAE) INHIBITOR, IN COMBINATION WITH TEMOZOLOMIDE AND IRINOTECAN IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS

Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)

[redacted]

For COG PEP-CTN Operations and Data/Statistics Contacts see: http://members.childrensoncologygroup.org

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[redacted]

STUDY COMMITTEE (CONTINUED)

[redacted]

AGENT NSC# AND IND#s

Agent Supplied by Takeda Pharmaceuticals:
Pevonedistat (MLN4924, NSC # 793435)

Commercial Agents:
Temozolomide (Temodar®, Temodal®; NSC# 362856)
Irinotecan (Camptosar®; NSC# 616348)

[redacted]

IND Sponsor: COG

SEE SECTION 8.3.6 AND 8.4.6 FOR SPECIMEN SHIPPING ADDRESSES

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ABSTRACT

Pevonedistat is a novel first-in-class NEDD8 activating enzyme (NAE) inhibitor that blocks the degradation of a subset proteins which would normally be degraded by the 26S proteasome. Pevonedistat is more specific than previous proteasome inhibitors because it blocks the degradation of Cullin-RING ligases (CRL), narrowing the targets to only a handful of key regulatory proteins important in cell survival. Phase 1 studies of pevonedistat in adults with hematologic and non-hematologic malignancies have shown promising results and tolerability. Pre-clinical studies demonstrate anti-tumor activity in a variety of pediatric tumors including neuroblastoma, Ewing sarcoma, Wilms tumor, rhabdomyosarcoma, and glioblastoma. *In vivo* experiments demonstrate additive properties of pevonedistat in combination with irinotecan and alkylating agents. We will use a rolling six design to conduct a phase 1 trial of pevonedistat in combination with irinotecan and temozolomide in pediatric patients with recurrent or refractory solid and brain tumors. The objectives of this study are to determine the maximum tolerated dose (MTD) and recommended Phase 2 dose (RP2D) of pevonedistat in combination with irinotecan and temozolomide, as well as to describe the toxicities, pharmacokinetic, and pharmacodynamic properties of this combination.

EXPERIMENTAL DESIGN SCHEMA

Cycle 1 (28 days)					
	Pevonedistat	Irinotecan	Temozolomide	Cefixime*	Evaluation
Day 1	X				
…					
Day 4					
…					
Day 6				X	
Day 7				X	
Day 8	X	X	X	X	
Day 9		X	X	X	
Day 10	X	X	X	X	
Day 11		X	X	X	
Day 12	X	X	X	X	
Day 13				X	
Day 14				X	
Day 15				X	
…					
Day 27				X	
Day 28				X	X

Subsequent Cycles (21 days)					
	Pevonedistat	Irinotecan	Temozolomide	Cefixime*	Evaluation
Day -1				X	
Day 0				X	
Day 1	X	X	X	X	
Day 2		X	X	X	
Day 3	X	X	X	X	
Day 4		X	X	X	
Day 5	X	X	X	X	
Day 6				X	
Day 7				X	
Day 8				X	
…					
Day 20				X	
Day 21				X	X

* Cefixime will be administered starting at least two days prior to the start of irinotecan, during, and 3 days after the last dose of irinotecan of each cycle for a total of at least 10 days.
- For Cycle 1, cefixime will be administered on Days 6-15 and Days 27-28.
- For Cycles 2+, cefixime will be administered on Days -1 through 8 and Days 20-21.

Days 27 and 28 of Cycle 1 are the same as Days -1 and 0 of Cycle 2. Days 20 and 21 of Cycles 2+ are the same as Days -1 and 0 of subsequent cycles.

NOTE: Once PCP Prophylaxis begins on Cycle 1 Day 8, patient should continuously receive PCP prophylaxis per the prescribed schedule until the end of treatment. See Section 5.1 for more details.

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of pevonedistat administered as an intravenous infusion on Days 1, 8, 10, and 12 of a 28-day cycle (Cycle 1), and on Days 1, 3, and 5 of a 21-day cycle (Cycle 2 and beyond) in combination with irinotecan (administered as an intravenous infusion on Days 8-12 of Cycle 1 and Days 1-5 of Cycles 2+) and temozolomide (administered orally on Days 8-12 in Cycle 1 and Days 1-5 of Cycles 2+) in children with recurrent or refractory solid tumors, including CNS tumors and lymphoma.

1.1.2 To define and describe the toxicities of pevonedistat administered on this schedule.

1.1.3 To characterize the pharmacokinetics of pevonedistat in children with recurrent or refractory cancer.

1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of pevonedistat within the confines of a phase 1 study.

1.2.2 To assess the biologic activity of pevonedistat.

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

Pevonedistat (MLN4924) is a novel chemotherapy agent; it blocks the degradation of proteins that would normally be degraded by the 26S proteasome, the major mechanism of protein removal in the cell. Pevonedistat is more specific than previous proteasome inhibitors because it blocks the degradation of Cullin-RING ligases (CRL), narrowing the targets to only a handful of key regulatory proteins important in cell survival. Phase 1 studies of pevonedistat in adults with both hematologic and non-hematologic malignancies have shown promising results with minimal adverse effects at the proposed dose level.[1-5] However, there is limited data with respect to pediatric malignancies. Preliminary data from the Pediatric Preclinical Testing Program (PPTP) showed promising results when tested against both the PPTP *in vitro* cell line panel as well as solid tumor xenografts.[6]

Neddylation is an ATP-dependent process which is involved in the regulation of intracellular protein destruction. Similar to the ubiquitin system, the process of neddylation is controlled by a multistep process involving one activation enzyme (E1), several ubiquitin conjugating enzymes (E2), and many ubiquitin ligases (E3). Recent studies have shown that by inhibiting the E1 NEDD8 activating enzyme (NAE), pevonedistat is able to disrupt cancer cell proliferation by interfering with Cullin-RING ligases.[7-10] Cullin-RING ligases are part of the ubiquitination cascade, a process that results in the timed degradation of many important proteins in the cell cycle progression, cell cycle checkpoint activation, and

cell signaling.

In many malignant cell types, pevonedistat leads to re-replication of DNA in S-phase and resultant cell death. Inhibition of NAE results in an increase in CRL substrates Cdt1 and Nrf-2, both of which contribute to cell-cycle progression.[11] Experiments in cancers of the prostate, lung, and colon, as well as glioblastoma cells have shown that Cdt1 is stabilized and cells continues to initiate DNA replication, resulting in multiple areas of DNA re-replication.[12] By blocking Cdt1 and Nrf-2 degradation, pevonedistat allows DNA replication to continue without cell division.[7] This is thought to activate both apoptosis and senescence pathways.[7,11]

In other cell types such as non-Hodgkin lymphoma (NHL), the induction of tumor cell apoptosis by pevonedistat involves inhibition of NF-κB.[13] The NF-κB pathway is involved in multiple cellular activities, including the induction of anti-apoptotic proteins following chemotherapy treatment. NAE regulates the ubiquitination and degradation of IκB-α. If NAE is inactivated, IκB-α is stabilized and NF-κB is unable to assert its anti-apoptotic effects, promoting cell death in malignant lymphoma cells.[13]

2.1.1 Irinotecan/Temozolomide Combination

Due to significant preclinical antitumor activity and non-overlapping toxicities, irinotecan and temozolomide in combination has been used in pediatric phase 1-2 trials in patients with recurrent or refractory solid and central nervous system tumors, and is broadly applicable. The combination has been well-tolerated.[14-22] In *in vitro* studies, irinotecan has shown to be synergistic with pevonedistat.[23] In ADVL0414, irinotecan and temozolomide were combined along with vincristine in children with refractory solid tumors.[22] Zero of six patients in ADVL0414 experienced dose limiting toxicity (DLT) at the highest doses studied (irinotecan 90 mg/m^2/day on Days 1-5, temozolomide 150 mg/m^2/day on Days 1-5, vincristine 1.5 mg/m^2 on Day 1). This is a similar irinotecan/temozolomide dosing schedule to what we propose in this study. Irinotecan and temozolomide in combination with temsirolimus was studied in ADVL0918.[15] Irinotecan 50 mg/m^2/dose and temozolomide 100 mg/m^2/dose were combined with temsirolimus at 25 mg/m^2 intravenous (IV) infusion on Days 1 and 8. The DLT was hypercholesterolemia in patients who were receiving steroids, and most likely attributable to the temsirolimus. None of the additional 6 patients treated with irinotecan 50 mg/m^2/dose, temozolomide 100 mg/m^2/dose, and temsirolimus 35 mg/m^2 IV on Days 1 and 8 experienced Cycle 1 DLT. This is a similar irinotecan/temozolomide dosing schema to what we propose in this study.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

2.2.1.1 Combination studies of pevonedistat

a. Irinotecan: *In vitro* combinations of pevonedistat and irinotecan (SN-38) in 4 solid tumor cell lines show that irinotecan is synergistic in 2 of the cell lines (HCT-116 and U2OS), and additive in 1 cell line (A549). Among 13 agents tested in combination with pevonedistat, irinotecan ranked among the top quartile for synergy (Figure 1).[24]

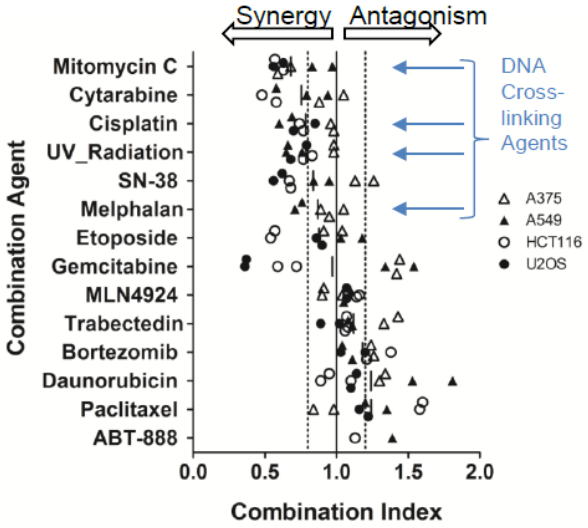


Figure 1. In vitro combinations of pevonedistat + standard of care agents.

Irinotecan was also additive with pevonedistat in *in vivo* models. Two colorectal xenograft models (HCT-116 and HT-29) exhibited an additive and subadditive combination effect, respectively. Balb/c nude mice were used to create subcutaneous xenografts of HCT-116 and HT-29. Pevonedistat was dosed subcutaneously (SubQ) on the following two 21-day dosing schedules: 30 mg/kg BID for 21 days and 90 mg/kg BID twice weekly for 21 days (dosing on Days 1, 4, 8, 11, 15, 18). Irinotecan was concurrently dosed intraperitoneally (IP) at 10 mg/kg twice weekly. Both dosing schedules exhibited additive and subadditive combination effects for HCT-116 and HT-29, respectively (Direct communication, Takeda Pharmaceuticals International Co.).

b. Alkylating agents: *In vitro* combinations of pevonedistat and standard chemotherapeutics show that the effect of adding alkylating agents is synergistic (Figure 1) (Direct communication, Takeda Pharmaceuticals International Co.). Of all combination agents tested, as a class, alkylating agents show the most synergy with pevonedistat. Alkylating agents tested include: dacarbazine, mitomycin C, cisplatin, carboplatin, and melphalan.

Both temozolomide and dacarbazine are triazine alkylating agents which are converted to the active alkylating metabolite (methyl-triazene-1-yl)-imidazole-4-carboxamide (MTIC). As described above, due to both its tolerability and effectiveness, temozolomide, in combination with irinotecan, is a common chemotherapy agent used in pediatric patients with relapsed or refractory disease.

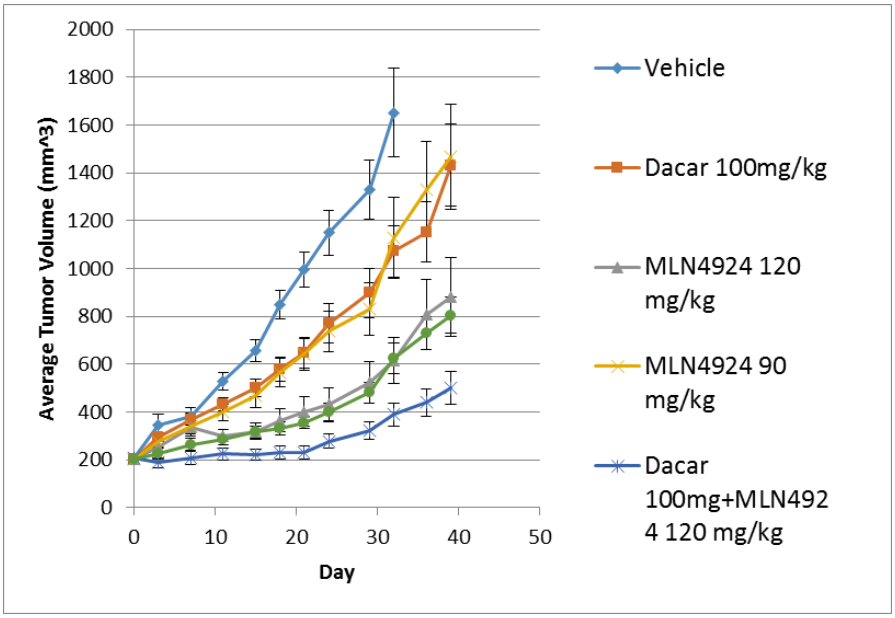


Figure 2. Combination of pevonedistat + dacarbazine in a primary human melanoma xenograft model PHTX-50M.

In vivo melanoma xenograft models demonstrate an additive cytotoxic effect when pevonedistat and dacarbazine are used together. In the *in vivo* studies, dacarbazine was dosed IP at 100 mg/kg for 5 days and pevonedistat was dosed BID twice weekly at either 90 mg/kg or 120 mg/kg. Additive effects were seen at both dose levels of pevonedistat (Figure 2) (Direct communication, Takeda Pharmaceuticals International Co.).

2.2.1.2 Pediatric *in vitro* and xenograft data

a. *In vitro* data from the Pediatric Preclinical Testing (PPTP): Pevonedistat showed promising results when tested against the PPTP in an *in vitro* cell line panel. The median relative IC_{50} (rIC_{50}) was 0.14 µM (range, 0.015 - 0.68 µM). The Ewing sarcoma panel was the most sensitive to pevonedistat, with an IC_{50} of 31 nM. The neuroblastoma panel had a median IC_{50} of 287 nM. Data from the PPTP shows that pevonedistat treatment resulted in significant differences in event free survival (EFS) in 61% of solid tumor xenografts (20/33), including Wilms (2 of 3 xenografts), rhabdomyosarcoma (2 of 5 xenografts), neuroblastoma (1 of 4 xenografts), and glioblastoma (4 of 4 xenografts). Twenty-nine percent (9/31) of evaluable solid tumor xenografts treated with pevonedistat exhibited intermediate activity, as defined by an increase in the ratio of the median time to event (EFS T/C values >2). Among the solid tumor xenograft panel, the best response was progressive disease with growth delay. This was observed in glioblastoma (4 of 4), Wilms (3 of 3), neuroblastoma (3 of 4), and rhabdomyosarcoma (2 of 5). Tumor tissue of all xenografts treated with pevonedistat showed a marked decrease in neddylated Cullin proteins, regardless of sensitivity. In our neuroblastoma xenograft experiments there

was a significant decrease in tumor weight between control and pevonedistat treated mice. Control mice had an average tumor weight of 1.6 mg ± 0.8 mg versus mice treated with pevonedistat which had average tumor weights of 0.5 mg ± 0.4 mg ($p<0.05$).[25]

b. Additional *in vitro* data: Our preliminary data shows that neuroblastoma cell lines are sensitive to pevonedistat with an IC_{50} of 0.2-7.6 µM (Table 1). Treatment of the neuroblastoma cell lines LAN5, CHP212, and SHEP with pevonedistat resulted in a biphasic dose response curve due to increases in cell size with increasing drug concentrations. We are currently testing these cells to determine if they undergo re-replication, one of the mechanisms of pevonedistat-mediated cell death in carcinomas. Drug combination analysis with pevonedistat and doxorubicin and etoposide are ongoing in a variety of solid tumor cell lines.

Table 1. Potency in Neuroblastoma Cell Lines

NB Cell Line	IC_{50} (µM)	N-myc amplified	p53 status
IMR-32	0.4	Y	WT
LAN-5	0.2	Y	WT
SHEP	2.6 and 4.8	N	WT
CHP212	7.6	Y	WT
SK-N-AS	0.5 and 1.7	N	Mutant

2.2.2 Animal Toxicology

The dose-limiting toxicities (DLTs) of pevonedistat administered as a 30 minute IV infusion or SubQ injection for 2 cycles (5 days of dosing followed by 14 day rest) or 5 cycles (4 doses given every other day followed by 14 day rest) in rats and dogs were GI toxicity and bone marrow suppression. Myocardial toxicity, injection site necrosis, enteropathy, and sepsis were seen at doses above the maximum tolerated dose (MTD). Most DLTs resolved after the 14 day rest period. Other effects observed were decreased trabecular bone formation, serum chemistry changes, an acute phase response, increased developmental risk to the fetus or embryo, and degeneration of the seminiferous epithelium of the testes. Most adverse events were reversed or reversing at completion of the 14 day rest period.[26]

2.2.3 Preclinical Pharmacokinetic Studies

Pevonedistat selectively inhibits the NAE with a $K_i \leq 1$ nM. When tested amongst a panel of 11 kinases, pevonedistat was 2,000 times more selective for NAE. Tumor cells treated with pevonedistat showed a decrease in NEDD8 Cullin levels and an increase in CDL substrates, consistent with inhibition of NAE.[26]

2.3 Adult Studies

2.3.1 Phase 1 Studies

Phase 1 studies of pevonedistat in adults with both hematologic and non-hematologic malignancies have shown promising results and tolerability on an intermittent dosing schedule.[1-5]

In a phase 1 study of pevonedistat in adults with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML), when pevonedistat was administered on Days 1, 3, and 5 (schedule A) every 21 days, the maximum tolerated dose (MTD) was 59 mg/m^2 and the DLT was hepatotoxicity. Out of 23 patients treated at or below the MTD, there were 2 complete responses (CRs) and 2 partial responses (PRs) for an overall response rate of 17%. When pevonedistat was administered on Days 1, 4, 8, and 11 (schedule B) every 21 days, the MTD was 83 mg/m^2 and the DLT was multi-organ failure. Out of 19 patients treated, there were 2 PRs for a response rate of 10%.[5]

In a phase 1 trial of pevonedistat monotherapy in adult patients with advanced solid tumors, pevonedistat was well tolerated on an intermittent dosing schedule.[3] In patients receiving pevonedistat administered on Days 1-5 (schedule A) the MTD was 50 mg/m^2 and the DLT was grade 3 elevated transaminases (n=3). Additionally, two patients died during Cycle 1 of treatment-related multi-organ failure (including liver failure) (n=1) and disease progression (n=1). Due to the multi-organ failure and DLTs, the Days 1-5 continuous dosing schedule was deemed intolerable. In schedule B, patients received pevonedistat on Days 1, 3, and 5 of a 21-day cycle along with oral dexamethasone pre-treatment. The MTD was 50 mg/m^2 and the DLTs were elevated transaminases (n=1) and hyperbilirubinemia (n=2). In schedule C, patients received pevonedistat without oral dexamethasone on Days 1, 3, and 5 of a 21-day cycle. The MTD was 67 mg/m^2 and the DLTs were hyperbilirubinemia and elevated AST (n=2). In this phase 1 trial of pevonedistat in adults with advanced solid tumors, the majority of patients had colorectal cancer (n=11), melanoma (n=9), or breast cancer (n=8). Fifty-three percent (n=26) of patients experienced Grade ≥ 3 AEs: anemia (n=5), elevated ALT (n=3), and 2 patients each for the following: congestive heart failure, dyspnea, fatigue, elevated AST, hyperbilirubinemia, hyponatremia, hypokalemia, hypophosphatemia, nausea, vomiting. One patient on schedule A had a partial response and 80% (n=12/15) of evaluable patients on schedule B and 69% (n=11/16) on schedule C had stable disease with a median duration of 2 (range, 0.5-7.4) and 2.1 (range, 0.6-3.6) months, respectively.

Similar results were shown in a phase 1 trial of pevonedistat in 37 patients with metastatic melanoma.[1] Patients received pevonedistat IV on either Days 1, 4, 8, 11 (schedule A, 26 patients) or 1, 8, 11, 15 (schedule B, 11 patients) of a 21 day cycle. The MTD was determined to be 209 mg/m^2, with DLTs of Grade 3 hypophosphatemia, myocarditis, renal failure and increased creatinine. The most common AEs were fatigue (68%), diarrhea (49%), anemia (41%), myalgia (41%), nausea (35%), constipation (32%), vomiting (32%), arthralgia (30%), decreased appetite (30%), dizziness (27%), and peripheral neuropathy (27%). Thirty-eight percent of patients experienced at least one SAE, 16% of which were drug related.

Pevonedistat was also tested in a phase 1 study for patients with relapsed/refractory multiple myeloma or lymphoma.[4] In the 44 patients treated on this study, the MTD was found to be 110 mg/m^2 (Days 1, 2, 8, 9 of a 21 day cycle) and 196 mg/m^2 (Days 1, 4, 8, 11 of a 21 day cycle). DLTs were febrile neutropenia, transaminase elevations, muscle cramps, and thrombocytopenia. There were no treatment related deaths. The most common AEs were fatigue and nausea.

Among the phase 1 monotherapy studies, 1 patient had a DLT of Grade 4 cardiac

failure which was attributed to be related to pevonedistat and subsequently resolved. This patient received 147 mg/m^2 of pevonedistat. Myocardial ischemia and atrial fibrillation occurred in 3 (1%) patients. All of the arrhythmias experienced by patients on the phase 1 studies were supraventricular, and all but 1 were unrelated. The patient with related atrial fibrillation had pre-existing risk factors for cardiac disease. In the phase 1 study in which pevonedistat was combined with azacitidine in elderly patients with AML, one patient experienced cardiac failure which was attributed as unrelated. Tachycardia was found to be an expected adverse drug reaction.[26]

There have been two phase 1 studies in adults of pevonedistat in combination with standard chemotherapy, one in patients with AML and another in patients with solid tumors. In a phase 1 study of pevonedistat in combination with azacitidine in elderly adults with AML who were considered unfit for conventional chemotherapy, the MTD of pevonedistat was 20 mg/m^2 in combination with azacitidine. Pevonedistat was administered on Days 1, 3, 5 of a 28-day cycle in combination with azacitidine 75 mg/m^2 on Days 1-5 and 8-9. Four patients experienced the DLT of increased transaminases. At least one adverse event (AE) was experienced by 64% (n=27) of patients. The most common AEs were febrile neutropenia (n=12), pneumonia (n=4), sepsis (n=3), pyrexia (n=2) and epistaxis (n=2). In 18 response-evaluable patients, there were 6 CRs (33%) 4 PRs (22%).[26]

The other combination study evaluated patients with advanced solid tumors treated with pevonedistat in combination with docetaxel (Arm 1), carboplatin lead-in and carboplatin + paclitaxel (Arm 2), and gemcitabine (Arm 3). Pevonedistat was administered on Days 1, 3, and 5 of a 21-day cycle in Arms 1 and 2, and on Days 1, 8, and 15 of a 28-day cycle for Arm 3. Fifty-eight patients were enrolled (Arm 1 = 22 patients, Arm 2 = 26 patients, Arm 3 = 10 patients), corresponding to 230 cycles of pevonedistat. The most common AEs were fatigue (48%), nausea (43%), AST increased (34%), anemia (34%), neutrophil count decreased (29%), constipation (28%), ALT increased (28%), and diarrhea (28%). Twelve patients experienced DLTs: 8 had increased LFTs, 3 had febrile neutropenia, and 1 had afebrile neutropenia. The MTDs for Arms 1 and 2 were 25 mg/m^2 and 20 mg/m^2 respectively. The MTD for Arm 3 was not calculated because the treatment arm was closed for intolerability. There were 7 total PRs, 3 each in Arm 1 and Arm 2 carboplatin + Paclitaxel, and 1 PR in Arm 2 lead-in with carboplatin.[26]

2.3.2 Phase 2 Studies

Two studies are currently enrolling.

- Study 2001: A Phase 2, randomized, controlled Open-Label Clinical study of the efficacy and safety of Pevonedistat plus Azacitidine versus single-agent azacitidine in patients with higher-risk myelodisplastic syndromes, chronic myelomococytic leukemia, and low-blast acute myelogenous leukemia.

- Study 1012: A phase 1/1b, Open-label Study of Pevonedistat (MLN4924, TAK-924) as Single Agent and in Combination with Azacitidine in adult East Asian patients with acute myeloid leukemia or myelodisplastic syndromes.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Pharmacokinetic (PK) studies of pevonedistat (25-83 mg/m^2/dose) in adults with non-hematologic malignancies demonstrated a half-life ($t_{½}$) of 5-8 hours,

maximum plasma concentration (C_{max}) of 106-1,340 ng/mL, and an area under the curve (AUC_{0-24h}) between 703 to 5,110 ng*hr/mL. PK studies in adults with hematologic malignancies at doses 25-147 mg/m^2 demonstrated a $t_{½}$ of 3-9 hours, C_{max} of 200-2,200 ng/mL, and an AUC_{0-24h} between 1,130-6,780 ng*hr/mL. In both adults with non-hematologic and hematologic malignancies, pevonedistat C_{max} and AUC_{0-24hr} generally increased dose dependently and there was no apparent accumulation following once-daily dosing.[27] Following IV administration, pevonedistat concentrations ascended rapidly and declined in a bi-exponential manner by 24 hours after the end of infusion. As the dose was increased, a third compartment of drug disposition began to emerge in patients with quantifiable drug concentrations beyond 24 hours post-infusion.[5]

Pharmacodynamic analyses of patients with hematologic and non-hematologic malignancies have shown that pevonedistat stabilizes IκB in peripheral blood mononuclear cells (PBMC) as well as increases Cdt-1 and Nrf-2 in skin biopsies from treated patients.[27]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

None

2.4.2 Pharmacology/Pharmacokinetics/Correlative Biological Studies

None

2.5 Overview of Proposed Pediatric Study

This is a phase 1 dose escalation of pevonedistat as a single agent and in combination with irinotecan and temozolomide for patients with refractory or recurrent solid tumors, including CNS tumors and lymphoma. Pevonedistat will be administered in combination with IV irinotecan and PO temozolomide in a 28-day cycle for Cycle 1 and 21-day cycles thereafter in Part A1 (patients ≥ 12 months and ≤ 21 years). Part A2 will enroll infants (≥ 6 months to < 12 months) one dose level behind the dose level at which the patients in Part A1 are enrolling, in order to maximize the safety for infant subjects. Pharmacokinetics will be obtained in all patients (see Section 8.3). Pharmacodynamic studies will be obtained in consenting patients (see Section 8.4).

A cycle of therapy is considered to be 28 days for the first cycle and 21 days for cycles thereafter. A cycle may be repeated 17 times, up to a total duration of therapy of 12 months.

Pevonedistat will be administered IV over 1 hour on Days 1, 8, 10, and 12 of a 28-day cycle for Cycle 1, and on Days 1, 3, and 5 of a 21-day cycle for Cycle 2 and beyond. After the initial dose of pevonedistat (Cycle 1 Day 1), subsequent doses will be given in conjunction with irinotecan and temozolomide. The MTD in adult phase 1 studies in adults given in combination with standard chemotherapy with advanced solid tumors treated on this schedule is 20-25 mg/m^2. Since in this study pevonedistat will be combined with irinotecan and temozolomide, a relatively well-tolerated regimen, the starting dose will be 15 mg/m^2, 75% of the adult MTD. Part A2 will open to enrollment on Dose Level 1 (15 mg/m^2) once Part A1 has escalated to Dose Level 2 (20 mg/m^2). In order to obtain single agent PK data, pevonedistat will be given as a single dose one week prior to initiating combination therapy with irinotecan and temozolomide.

The industry partner does not have plans to develop pevonedistat as a single agent in

pediatrics. Thus, this study is designed to determine the safety and pharmacokinetics of pevonedistat alone and in combination with irinotecan and temozolomide.

2.6 **Rationale for Amendment #5 (addition of dose level 4)**

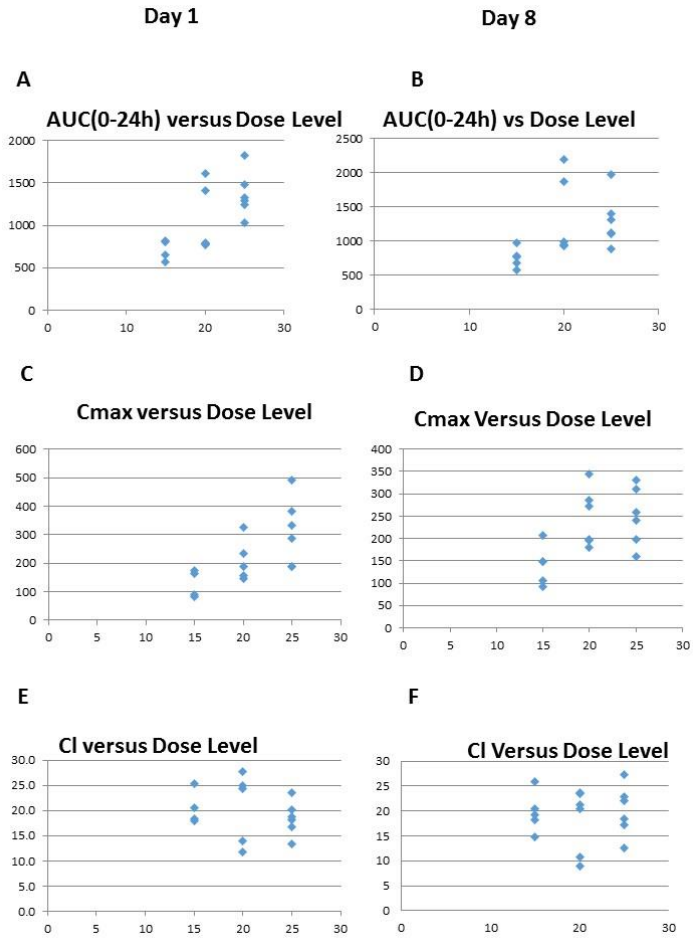
Pevonedistat, a first in class inhibitor of NEDD8 activating enzyme (NAE), prevents the activation of Cullin-RING ligases (CRL) necessary for proteasome mediated degradation of key regulatory proteins important in cell survival. In adults with solid tumors, the maximum tolerated dose (MTD) in combination with chemotherapy is 20-25 mg/m^2. [28,29]

As a single agent in adults with MDS/AML the MTD for pevonedistat infusions on days 1, 3, and 5 per cycle was determined to be 59 mg/m^2 and for melanoma or advanced solid tumors, was determined to be 67 mg/m^2. The recommended phase 2 dose for pevonedistat monotherapy for that schedule is 50mg/m^2.[1,30] In adults, the predominant dose limiting toxicity (DLT) was hepatoxicity.

In our current Phase 1 Study of Pevonedistat (MLN4924) a NEDD8 Activating Enzyme Inhibitor, in Combination with Temozolomide (TMZ) and Irinotecan (IRN) in Pediatric Patients with Recurrent or Refractory Solid Tumors (ADVL1615), 18 patients have enrolled and all were eligible and evaluable for cycle 1 dose limiting toxicity (DLT) assessment. Six patients each enrolled on pevonedistat dose levels 1 (15mg/m^2), 2 (20mg/m^2), and 3 (25mg/m^2). No pediatric patients experienced a DLT, and only 1 patient each experienced grade 3 elevated AST and elevated ALT, which resolved and did not meet criteria for dose-reduction.[33]

The pharmacokinetics (PK) of pevonedistat were similar in adult and pediatric studies. In our pediatric study, the mean area under the curve (AUC) at the 25 mg/m^2 dose level on day 8 (in combination with irinotecan and temozolomide) was 1296 hr•ng/mL, half-life (T ½) was 5-6 hours, time to maximum concentration (Tmax) was 1 hour, and average clearance was 20 L/hr/m^2, comparable with adult trials (Figure 1).[31] Both AUC and maximum concentration (Cmax) increased with dose level, but unlike the adult data, the increase appeared to be greater than dose-proportional. This was reflected in the Day 1 clearance which showed a small decrease with dose suggesting non-linear clearance.

Given that the recommended Phase 2 dose of pevonedistat as a monotherapy for the current schedule is 50 mg/m^2 and the observed good tolerability of the combination of pevonedistat, irinotecan and temozolomide in pediatric patients at 25 mg/m^2, we propose amending our trial to include a dose level 4 of 35 mg/m^2. Based on our pediatric PK data, we expect this dose level will result in a 40% increase in AUC and Cmax, equivalent to approximately an adult dose of 45 mg/m^2. If dose level 4 proves intolerable, we propose opening an expanded PK cohort at the 25 mg/m^2 dose (dose level 3).



3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Oncology Patient Enrollment Network (OPEN), a web-based registration system available on a 24/7 basis. It is integrated with the NCI Cancer Trials Support Unit (CTSU) Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the RAVE database.

Access requirements for OPEN:
Investigators and site staff will need to be registered with CTEP and have a valid and active Cancer Therapy Evaluation Program-Identity and Access Management (CTEP-IAM) account (check at < https://ctepcore.nci.nih.gov/iam/index.jsp >). This is the same account (user id and password) used for credentialing in the CTSU members' web site. To perform registrations in OPEN, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org.

3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To

access the Studies Requiring Reservations page:

1. Log in to https://open.ctsu.org/open/
2. Click the **Slot Reservation** Tab. *The Site Patient page opens.*
3. Click the **Report** Tab. *The Slot Reservation Report opens. Available Slots are detailed per study strata.*

3.2 IRB Approval

NCI Pediatric CIRB approval or local IRB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit CIRB/IRB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the Regulatory Tab.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.
For general (non-regulatory) questions, call the CTSU General Helpdesk at 1-888-823-5923 or contact CTSU by email at ctsucontact@westat.com.

Study centers can check the status of their registration packets by accessing the Site Registration Status page on the CTSU Member's Website under the Regulatory Tab. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

3.3 Patient Registration

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry in the OPEN system once authorization for the release of protected health information (PHI) has been obtained.

3.4 Reservation and Contact Requirements

Before enrolling a patient on study, a reservation must be made through the OPEN website and the Study Chair or Vice Chair should be notified. (The patient will need a COG patient ID number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

Reservations may be obtained 24-hours a day through the OPEN website.

3.5 **Informed Consent/Assent**

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

3.6 **Screening Procedures**

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through one of the following mechanisms: a) the COG screening protocol, b) an IRB-approved institutional screening protocol or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

3.7 **Eligibility Checklist**

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

3.8 **Institutional Pathology Report**

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

3.9 **Study Enrollment**

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the COG Study Research Coordinator, or the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

3.10 **Dose Assignment**

The dose level will be assigned via OPEN at the time of study enrollment.

4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT), and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.

4.1 Inclusion Criteria

4.1.1 Age:

4.1.1.1 **Part A1:** Patients must be ≥ 12 months and ≤ 21 years of age at the time of study enrollment.

4.1.1.2 **Part A2:** Patients must be ≥ 6 months and < 12 months of age at the time of study enrollment. Patients will enroll one dose level behind the dose level at which patients in Part A1 are enrolling.

4.1.2 Diagnosis: Patients with recurrent or refractory solid tumors, including CNS tumors and lymphoma, for which no standard therapy is available are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG.

4.1.3 Disease Status: Patients must have either measurable or evaluable disease (see Section 12.2 and Section 12.3 for definitions).

4.1.4 Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

4.1.5 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (see Appendix I). **NOTE:** Neurologic deficits in patients with CNS tumors must have been relatively stable for at least 7 days prior to study enrollment. Patients who are unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of

assessing the performance score.

4.1.6 Prior Therapy

4.1.6.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the numerical eligibility criteria are met, e.g., blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. At least 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea). See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study assigned Research Coordinator prior to enrollment.

b. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): ≥ 7 days after the last dose of agent. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study assigned Research Coordinator prior to enrollment.

c. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.

d. Corticosteroids: See Section 4.2.2.1. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid.

e. Hematopoietic growth factors: ≥ 14 days after the last dose of a long-acting growth factor (e.g., pegfilgrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair and the study assigned Research Coordinator.

f. Interleukins, Interferons and Cytokines (other than Hematopoetic Growth Factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoietic Growth Factors).

g. Stem cell Infusions (with or without TBI):
- Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 84 days after infusion and no evidence of GVHD.
- Autologous stem cell infusion including boost infusion: ≥ 42 days.

h. Cellular Therapy: ≥ 42 days after the completion of any type of cellular therapy (e.g., modified T cells, NK cells, dendritic cells, etc.)

i. XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.

j. Radiopharmaceutical therapy (e.g., radiolabeled antibody, 131I-MIBG): ≥ 42 days after systemically administered radiopharmaceutical therapy.

k. Patients must not have received prior exposure to pevonedistat. Patients with prior exposure to irinotecan or temozolomide are eligible.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function defined as:

a. For patients with solid tumors without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm^3
- Platelet count ≥ 100,000/mm^3 (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment).
- Hemoglobin ≥ 8 g/dL

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in Section 4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 patients on Part A1 must be evaluable for hematologic toxicity for the dose-escalation part of the study. If dose-limiting hematologic toxicity is observed, all subsequent patients enrolled must be evaluable for hematologic toxicity.

4.1.7.2 Adequate Renal Function defined as:
- Creatinine clearance or radioisotope GFR ≥ 70 mL/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	**Maximum Serum Creatinine (mg/dL)**	
	Male	**Female**
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.1.7.3 Adequate Liver Function defined as:
- Bilirubin (sum of conjugated + unconjugated) ≤ upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.
- SGOT (AST) ≤ 150 U/L. For the purpose of this study, the ULN for SGOT is 50 U/L.
- Serum albumin ≥ 2.7 g/dL

4.1.7.4 Adequate Cardiac Function defined as:
- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by gated radionuclide study.
- No supraventricular arrhythmia on EKG
- Prolonged rate corrected QT (QTc) interval < 500 msec

4.1.7.5 Adequate Pulmonary Function defined as:
- Pulse oximetry > 94% on room air if there is clinical indication for determination (e.g. dyspnea at rest).

4.1.7.6 Adequate Neurologic Function defined as:
- Patients with seizure disorder may be enrolled if on non-enzyme inducing anticonvulsants and well controlled. See Section 4.2.6.4 for further details.
- Nervous system disorders (CTCAE version 5.0) resulting from prior therapy must be ≤ Grade 2, with the exception of decreased tendon reflex (DTR). Any grade of DTR is eligible.

4.1.7.7 Adequate Coagulation defined as:
- INR ≤ 1.5

4.1.8 Informed Consent: All patients and/or their parents or legally authorized representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

4.2.1.1 Pregnant or breast-feeding women will not be entered on this study because there is not yet available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal.

4.2.1.2 Males or females of reproductive potential may not participate unless they have agreed to practice 1 highly effective and 1 additional effective (barrier) method of contraception at the same time during the entire study treatment period and through 4 months after the last dose of study drug, or agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), withdrawal, spermicides only,

and lactational amenorrhea are not acceptable methods of contraception.

4.2.2 Patients with uncontrolled high blood pressure (i.e., systolic/diastolic blood pressure > 99th percentile) are not eligible. See Appendix XII for more details.

4.2.3 Patients with known cardiopulmonary disease are not eligible. Cardiopulmonary disease is defined as:

- Cardiomyopathy other than chemotherapy related changes in cardiac function that meet the eligibility requirements in Section 4.1.7.4.
- Clinically significant arrhythmia:
    1. History of polymorphic ventricular fibrillation or torsade de pointes,
    2. Permanent atrial fibrillation [a fib], defined as continuous a fib for ≥ 6 months,
    3. Persistent a fib, defined as sustained a fib lasting > 7 days and/or requiring cardioversion in the 4 weeks before screening,
    4. Grade 3 a fib defined as symptomatic and incompletely controlled medically, or controlled with device (e.g. pacemaker), or ablation and
    5. Patients with paroxysmal a fib or < Gr 3 a fib for period of at least 6 months are permitted to enroll provided that their rate is controlled on a stable regimen.
- Implantable cardioverter defibrillator;
- Moderate to severe aortic and/or mitral stenosis or other valvulopathy (ongoing);
- Pulmonary hypertension
- Congestive heart failure Class III or IV (See Appendix IX)

4.2.4 Patients with known hepatic cirrhosis or severe pre-existing hepatic impairment are not eligible.

4.2.5 Patients with uncontrolled coagulopathy or bleeding disorder are not eligible.

4.2.6 Concomitant Medications

4.2.6.1 Corticosteroids: Patients receiving corticosteroids who have not been on a stable or decreasing dose of corticosteroid for at least 7 days prior to enrollment are not eligible. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid (See Section 4.1.6.1.d).

4.2.6.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.6.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

4.2.6.4 Anticonvulsants: Patients must not have received enzyme-inducing anticonvulsants for at least 7 days prior to enrollment (see Appendix V for a list of enzyme-inducing and non-enzyme-inducing anticonvulsants).

4.2.6.5 Anti-GVHD agents post-transplant:
Patients who are receiving cyclosporine, tacrolimus or other agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial.

4.2.6.6 Patients who are receiving any investigational agent other than pevonedistat, including but not limited to androgens, supraphysiologic doses of corticosteroids, erythropoietin, eltrombopag, or romiplostim.

4.2.7 Drug Interaction:
Patients who have received drugs that are strong inducers of CYP3A4 within 14 days prior to study enrollment are not eligible. See Appendix VII for more details.

While on study, concomitant use of strong CYP3A4 inhibitors (see Appendix VII), BCRP inhibitors (cyclosporine, eltrombopag, gefitinib), and UGT1A1 inhibitors (diclofenac, ketoconazole, probenecid, silibinin, nilotinib, and atazanavir) should be avoided because of potential for increased irinotecan toxicity.

4.2.8 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.9 Patients who have received a prior solid organ transplantation are not eligible.

4.2.10 Patients with known human immunodeficiency virus (HIV) seropositive are not eligible.

4.2.11 Patients with known hepatitis B surface antigen seropositive or known or suspected active hepatitis C infection are not eligible. **NOTE:** Patients who have isolated positive hepatitis B core antibody (i.e., in the setting of negative hepatitis B surface antigen and negative hepatitis B surface antibody) must have an undetectable hepatitis B viral load. Patients who have positive hepatitis C antibody may be included if they have an undetectable hepatitis C viral load.

4.2.12 History of allergic reactions attributed to compounds of similar chemical or biologic composition as the study agents.

4.2.13 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

Cycle 1							
Cycle Day							
1	**6**	**8**	**9**	**10**	**11**	**12**	**28**
	Cefixime (Days 6 – 15, 27 – 28) ----------→						
		TEMO	TEMO	TEMO	TEMO	TEMO	Eval
		IRIN	IRIN	IRIN	IRIN	IRIN	
Pevonedistat		**Pevonedistat**		**Pevonedistat**		**Pevonedistat**	
		PCP prophylaxis					
IRIN: Irinotecan; TEMO: temozolomide							

Cycle 2 and beyond							
Cycle Day							
-1	**0**	**1**	**2**	**3**	**4**	**5**	**21**
Cefixime (Days -1 to 8, 20 – 21) ----------→							
		TEMO	TEMO	TEMO	TEMO	TEMO	Eval
		IRIN	IRIN	IRIN	IRIN	IRIN	
		Pevonedistat		**Pevonedistat**		**Pevonedistat**	
		PCP prophylaxis					
IRIN: Irinotecan; TEMO: temozolomide							

See Appendix XIII for Therapy Delivery Maps for Cycle 1 and all subsequent cycles.

A cycle of therapy is considered to be 28 days for Cycle 1 and 21 days for Cycle 2 and subsequent cycles. Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from protocol therapy. Patients may continue on protocol therapy for up to 17 cycles (approximately 12 months).

Pevonedistat will be administered intravenously over 60 minutes on Days 1, 8, 10, and 12 of Cycle 1 and on Days 1, 3, and 5 of Cycles 2+ (starting dose is 15 mg/m^2 [Dose Level 1]).

Cefixime will be administered starting at least two days prior to the start of irinotecan, during, and 3 days after the last dose of irinotecan of each cycle for a total of at least 10 days.

- For Cycle 1, cefixime will be administered on Days 6-15 and Days 27-28.
- For Cycles 2+, cefixime will be administered on Days -1 through 8 and Days 20 through 21.

Days 27 and 28 of Cycle 1 are the same as Days -1 and 0 of Cycle 2. Days 20 and 21 of Cycles 2+ are the same as Days -1 and 0 of subsequent cycles.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle.

Method of Administration: Patients with solid tumors, including CNS tumors and lymphoma, will receive pevonedistat IV over one hour. In Cycle 1, pevonedistat will be administered as a single agent on Day 1 and in combination with oral temozolomide and IV irinotecan on Days 8, 10, and 12. In Cycles 2+, pevonedistat will be administered in combination with oral temozolomide and IV irinotecan on Days 1, 3, and 5 (see Appendix IV for temozolomide dosing nomogram and Section 9.4.4 for administration instructions for patients who cannot swallow temozolomide capsules whole). Irinotecan is administered

over 90 minutes one hour after temozolomide. Pevonedistat is administered over 60 minutes at the completion of irinotecan infusion. If emesis occurs within 30 minutes of taking a dose of temozolomide, then the dose may be repeated once. If emesis occurs after 30 minutes, the dose should not be repeated.

CYCLE 1:

Temozolomide: 100 mg/m^2/dose (maximum dose 200 mg) PO daily x 5 on Days 8-12. See Appendix IV for BSA-based dosing nomograms using oral capsules.

Irinotecan: BSA-based dosing (below), IV over 90 minutes daily x 5 on Days 8-12 one hour after temozolomide.

IRINOTECAN IV 50 mg/m^2 dose level	
BSA (m^2)	Dose (mg)
0.25-0.29	8
0.3-0.34	12
0.35-0.39	15
0.4-0.44	18
0.45-0.49	22
0.5-0.54	24
0.55-0.59	28
≥ 0.6	50 mg/m^2

Pevonedistat*: IV over 60 minutes on Day 1 alone and on Days 8, 10, and 12 immediately after irinotecan. Starting dose is 15 mg/m2 (Dose Level 1). See Dose Escalation Schema in Section 5.4.

For infusion-related reactions consider premedication with diphenhydramine for subsequent doses and increasing infusion duration to 2 hours. Other supportive care measures may be used at the investigator's discretion.

CYCLES 2+:

Temozolomide: 100 mg/m^2/dose (maximum dose 200 mg) PO daily x 5 on Days 1-5. See Appendix IV for BSA-based dosing nomograms using oral capsules.

Irinotecan: BSA-based dosing (below), IV over 90 minutes daily x 5 on Days 1-5 one hour after temozolomide.

IRINOTECAN IV 50 mg/m^2 dose level	
BSA (m^2)	Dose (mg)
0.25-0.29	8
0.3-0.34	12
0.35-0.39	15
0.4-0.44	18
0.45-0.49	22
0.5-0.54	24
0.55-0.59	28
≥ 0.6	50 mg/m^2

Pevonedistat*: IV over 60 minutes on Days 1, 3, and 5 immediately after irinotecan. Starting dose is 15 mg/m2 (Dose Level 1). See Dose Escalation Schema

in Section 5.4.

For infusion-related reactions consider premedication with diphenhydramine for subsequent doses and increasing infusion duration to 2 hours. Other supportive care measures may be used at the investigator's discretion.

***NOTE:** If pevonedistat dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained. In Cycles 2+, a maximum of 3 doses of pevonedistat should not be exceeded.

Diarrhea prophylaxis: Cefixime or an available equivalent antibiotic will be used as diarrheal prophylaxis during all cycles. Cefixime (8 mg/kg/day as a single daily dose; maximum daily dose 400 mg) or Cefpodoxime (10 mg/kg/day, divided in two oral doses; maximum daily dose 400 mg for children < 12 years and maximum daily dose 800 mg for children ≥ 12 years) will be administered starting at least two days prior to the start of irinotecan and continuing for 3 days after the last dose of irinotecan of each cycle for a total of 10 days.

Diarrhea treatment: See Appendix VIII.

Pneumocystis (PCP) prophylaxis: Patients must receive PCP prophylaxis starting on Cycle 1 Day 8, twice daily for 3 consecutive days a week (i.e., BID Friday, Saturday, and Sunday) every week, or per institutional practice, until the end of protocol therapy.

5.2 Criteria for Retreatment and Dose Delays

If pevonedistat dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained. In Cycles 2+, a maximum of 3 doses of pevonedistat should not be exceeded.

5.3 Criteria for Starting Subsequent Cycles

After Cycle 1 which is 28 days, a cycle may be repeated every 21 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0 or eligible to continue agent administration per the requirements in Section 6.0.

5.4 Dose Escalation Schema

5.4.1 Part A1: Inter-Patient Escalation

The starting dose will be 15 mg/m^2 (Dose Level 1) with dose levels for subsequent groups of patients as follows:

Dose Level	Pevonedistat Dose (mg/m^2)	Day(s) of Administration Cycle 1	Day(s) of Administration Cycles 2+
-1	10	1, 8, 10, 12	1, 3, 5
1*	**15**	**1, 8, 10, 12**	**1, 3, 5**
2	20	1, 8, 10, 12	1, 3, 5
3	25	1, 8, 10, 12	1, 3, 5
4	35	1, 8, 10, 12	1, 3, 5

* Starting Dose Level

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 10 mg/m^2 (Dose Level -1). If Dose Level -1 is not well tolerated, further de-escalation will not occur. The study will be closed

to accrual.

5.4.2 Part A2: Inter-Patient Escalation
Patients enrolling on Part A2 of the study will enroll one dose level behind the dose level at which patients in Part A1 are enrolling. Part A2 will open to enrollment on Dose Level 1 once Part A1 has escalated to Dose Level 2. Once the MTD is determined in Part A1, patients may enroll onto the Part A1 MTD. If at any time 2 or more evaluable patients at a lagging dose level experience a DLT, Part A2 will close to further accrual.

5.4.3 Intra-Patient Escalation
Intra-patient dose escalation is not allowed.

5.5 Grading of Adverse Events

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.6 Definition of Dose-Limiting Toxicity (DLT)

DLT will be defined as any of the following events. The DLT observation period for the purposes of dose-escalation will be the first cycle of therapy. Refer to Section 6.3 for specific criteria for patients < 12 months of age at the time of the non-hematological DLT.

Dose limiting hematological and non-hematological toxicities are defined differently.

5.6.1 Non-hematological dose-limiting toxicity for patients ≥ 12 months of age:

5.6.1.1 All Grade 3 or greater non-hematological toxicity not clearly related to the underlying disease and attributable to protocol therapy will be considered a DLT **except**:

- Grade 3 nausea and vomiting < 3 days duration
- Grade 3 elevation of ALT/AST/bilirubin, that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle. **NOTE:** For the purposes of this study the ULN for ALT is defined as 45 U/L and for AST is defined as 50 UL. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See section 5.6.3 and 6.2.4. See Appendix III for nomogram.
- Grade 3 hypophosphatemia (See section 6.2.5), hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.
- Grade 3 arthralgia/myalgia that returns to Grade ≤ 1 prior to the start of the next cycle or within 14 days of optimizing oral analgesics (whichever is shorter).

5.6.2 Non-hematological dose-limiting toxicity for patients < 12 months of age:

5.6.2.1 Any ≥ Grade 2 non-hematological toxicity not clearly related to the underlying disease and attributable to the protocol therapy will be considered a DLT with the specific exclusion of Grade 2 liver enzyme

elevation, including ALT/AST/bilirubin, that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle.

NOTE: For the purposes of this study the ULN for ALT is defined as 45 U/L and for AST is defined as 50 U/L. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See Appendix III for toxicity grading table.

5.6.2.2 Other pevonedistat-related non-hematologic toxicities Grade 2 or greater that, in the opinion of the investigator, require dose reduction or discontinuation of therapy with pevonedistat.

5.6.3 Non-hematological toxicity that causes a delay of ≥ 14 days between treatment cycles.

NOTE: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.6.4 Hematological dose limiting toxicity

5.6.4.1 Hematological dose limiting toxicity attributable to protocol therapy is defined as:

- Grade 4 neutropenia for > 7 days.
- Grade 4 anemia unexplained by underlying malignancy.
- Platelet count < 25,000/mm^3 on 2 separate days, or requiring a platelet transfusion on 2 separate days, within a 7 day period.
- Myelosuppression that causes a delay of > 14 days between treatment cycles.

NOTE: Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity.

6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

The Study Chair must be notified of any dosage modification or use of myeloid growth factor.

6.1 Dose Modifications for Hematological Toxicity (all age cohorts)

6.1.1 Patients who have dose-limiting neutropenia (Grade 4 neutropenia of > 7 days duration or delay in the start of the next cycle for > 14 days due to neutropenia) with no other dose-limiting toxicity should receive the same doses in the next cycle with myeloid growth factor support 24-48 hours after completion of irinotecan, temozolomide, and pevonedistat. Patients MUST NOT receive growth factor in the **first** cycle. If dose-limiting neutropenia recurs after myeloid growth factor is added, start the next cycle with a decrease in temozolomide to 75% of the original dose (75 mg/m^2/dose) on Days 1-5. If hematologic dose limiting toxicity occurs at 75% of the original dose of temozolomide, then pevonedistat dose level should be decreased to the next lower dose level. If dose limiting neutropenia recurs after use of growth factor and dose reductions of temozolomide and pevonedistat the patient should be removed from protocol therapy.

6.1.2 For dose-limiting thrombocytopenia, after counts recover, start the next cycle with

a decrease in temozolomide to 75% of the original dose (75 mg/m^2/dose) on Days 1-5. Patients should continue to receive the full doses of pevonedistat and irinotecan. If dose limiting thrombocytopenia occurs at 75% of the original dose of temozolomide, then pevonedistat dose level should be decreased to the next lower dose level and the irinotecan should be given at full dose.

6.1.3 Patients who have a dose-limiting hematological toxicity that does not resolve to eligibility parameters within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.2 Dose Modifications for Non-Hematological Toxicity (for patients ≥ 12 months)

6.2.1 Patients who have any dose-limiting non-hematological toxicity (as defined in Section 5.6.1) may continue on protocol therapy upon meeting eligibility lab requirements or baseline but should receive subsequent doses of pevonedistat at the next lower dose level. Irinotecan and temozolomide should be continued at the same dose.

6.2.2 If the same non-hematological dose-limiting toxicity recurs after one dose reduction, the patient must be removed from protocol therapy.

6.2.3 Patients who have a dose-limiting non-hematological toxicity that does not resolve to baseline or eligibility within 21 days after the planned start of the next treatment cycle must be removed from protocol therapy.

6.2.4 Pevonedistat dose modification for hepatic toxicity:

In all cycles, AST, ALT, and bilirubin should be checked prior to each dose of pevonedistat and then once weekly for the remaining weeks of the study. It is anticipated that LFTs (AST, ALT, and occasionally bilirubin) may be elevated for approximately 48 hours following the end of the 1st pevonedistat infusion. See Appendix III for toxicity grading table.

For Grade 2 or 3 AST, ALT, or bilirubin on or after Cycle 1 Day 8, pevonedistat should be held. Once the elevated AST, ALT, or bilirubin returns to ≤ Grade 1 by the end of the current cycle, then pevonedistat dose may be resumed at the same dose. If a dose is delayed due to increased LFTs, pevonedistat needs to be administered by Day 25 of Cycle 1 or Day 18 of subsequent cycles (within a cycle there should be a maximum of 13 days between doses).

For Grade 4 AST, ALT, or bilirubin on or after Cycle 1 Day 8, the pevonedistat dose should be held for the remainder of the cycle. If the elevated AST, ALT, or bilirubin return to ≤ Grade 1, then pevonedistat may be restarted at the next cycle at the next lower dose level.

Interventions for Dose Modifications Secondary to Elevated AST, ALT, or bilirubin	
Grade 2	Hold pevonedistat until resolved to ≤ Grade 1
Grade 3	Hold pevonedistat until resolved to ≤ Grade 1
Grade 4	Hold pevonedistat for remainder of cycle. For subsequent cycle resume at next lower dose level if resolved to ≤ Grade 1
For pevonedistat, a minimum of 1 full calendar day between any 2 doses should be maintained, and a maximum of 3 doses of pevonedistat within Cycles 2+ must not be exceeded. There should be a maximum of 13 days between doses within a given cycle.	

6.2.5 Pevonedistat dose modification for hypophosphatemia:

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

6.3 **Dose Modifications for Non-Hematological Toxicity (for patients < 12 months at the time of the DLT)**

Patients less than 12 months of age who have a ≥ Grade 2 non-hematological toxicity attributable to the study drug will have pevonedistat held as per Section 6.2 and this will be considered a DLT with the specific exclusion of Grade 2 liver enzyme elevation, including ALT/AST/bilirubin, that returns to Grade ≤ 1 or baseline prior to the time for the next treatment cycle (see Section 6.2.4). Patients should receive subsequent cycles of the drug but with dose modifications according to Section 6.2.

7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

7.1 **Concurrent Anticancer Therapy**

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

7.2 **Investigational Agents**

No other investigational agents may be given while the patient is on study.

7.3 **Supportive Care**

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. See Section 4.2.7 for drugs that should not be used concomitantly due to potential interactions with pevonedistat and irinotecan. See Section 5.1 and Appendix VIII for diarrhea prophylaxis and treatment recommendations.

7.4 **Growth Factors**

Growth factors that support platelet or white cell number or function can only be administered in accordance with Section 6.1.1 or for culture proven bacteremia or invasive fungal infection. The Study Chair should be notified before growth factors are initiated.

7.5 **Concomitant Medications**

Strong CYP3A4 inducers (see Appendix VII) are prohibited for the duration of the study. Strong inducers of CYP3A4 should be discontinued within 14 days prior to the first dose of pevonedistat.

Concomitant use of strong inhibitors of CYP3A4 (see Appendix VII), UGT1A1 inhibitors (such as diclofenac, ketoconazole, probenecid, silibinin, tacolimus, nilotinib, and atazanavir), and BCRP inhibitors (cyclosporine, eltrombopag, gefitinib) also should be avoided because of potential for increased irinotecan toxicity.

Acetaminophen may be used judiciously but should not exceed a dose of 37 mg/kg/day (maximum 2 g in 24 hours).

8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies must be obtained within fourteen (14) days prior to start of protocol therapy (repeat the tumor imaging if necessary). See Appendix XIII for Therapy Delivery Maps for Cycle 1 and all subsequent cycles.

Studies to be Obtained	For all patients		For patients ≥ 12 months ONLY	For patients < 12 months ONLY
	Pre-Study	During Cycle 1	Prior to Subsequent Cycles^	Prior to Subsequent Cycles^
History	X	X	X	X
Physical exam with vital signs[7]	X	Weekly	X	X
Height, weight, BSA	X		X	X
Performance status	X		X	X
CBC, differential, platelets	X	Twice weekly[1]	Weekly[1,2,3]	Weekly[1,2,3]
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly	X	Weekly
Creatinine	X	Weekly	X	Weekly
ALT, AST, bilirubin	X	Prior to each dose of pevonedistat, then weekly*	Prior to each dose of pevonedistat, then weekly*	Prior to each dose of pevonedistat, then weekly*
ECHO/EKG	X			
Albumin	X		X	X
Pulse Oximetry	X		X	X
Pregnancy test[4]	X		X	X
Tumor disease evaluation	X	End of Cycle 1	End of Cycle 2 then every other cycle x 2 then q 3 cycles[5]	End of Cycle 2 then every other cycle x 2 then q 3 cycles[5]
Bone Marrow Evaluation[8]	X	End of Cycle 1	End of Cycle 2 then every other cycle x 2 then q 3 cycles[5]	End of Cycle 2 then every other cycle x 2 then q 3 cycles[5]
Pharmacokinetics[6] (required)	X	X		
Pharmacodynamics (optional)	X	X		
INR	X			

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

[1] Twice weekly during Cycle 1. If patients have Grade 4 neutropenia or thrombocytopenia, CBCs should be checked at least every other day until recovery to Grade 3 or until the criteria for dose limiting toxicity are met.

[2] If patients develop Grade 4 neutropenia, CBCs should be checked every 3 to 4 days until recovery to Grade 3.

[3] If patients remain on study for > 4 cycles and ≥ Grade 3 cytopenias are not observed, then CBCs may be obtained at the start of subsequent cycles and as clinically indicated.

[4] Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable methods of birth control. All women of childbearing potential must have a pregnancy test done every cycle prior to initiation of a new cycle.

[5] Tumor disease evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

[6] See Section 8.3 for details.
[7] Vital signs should be checked prior to each pevonedistat infusion. Vital signs will also be assessed at the end of treatment.
[8] If a solid tumor patient is suspected to have or has a history of bone marrow involvement then a pre-study bone marrow biopsy and/or aspirate is required. This should then be repeated with each tumor disease evaluation if pre-study bone marrow was positive for metastatic disease.
*Check prior to each dose of pevonedistat, then weekly for remaining weeks of cycle. If patients have Grade 2, 3, or 4 ALT/AST/bilirubin on or after Cycle 1 Day 8, AST/ALT/bilirubin should be checked at least every other day until recovery to ≤ Grade 1. See Section 6.2.4 for more details.

8.2 Radiology Studies

8.2.1 Central Radiology Review for Response: Patients who respond (CR, PR) to therapy or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy will be centrally reviewed. COG Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the treating institution forward the requested images for central review. The central image evaluation results will be entered into RAVE for review by the COG Operations Center and for data analysis.

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the ImageInBox.

COG institutions that are not connected via the ImageInBox can send the images on CD ROM or USB flash drive. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1615), and date and shipped to Syed Aamer at the address below:

[redacted]

8.3 Pharmacokinetics (required)

8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of pevonedistat in children. Pharmacokinetic analysis will be conducted at a centralized laboratory using a GLP-validated liquid chromatography/tandem mass spectrometry (LC-MS/MS) assay.

Individual pevonedistat plasma concentration-time data will be analyzed using standard noncompartmental methods. The following PK parameters of pevonedistat will be estimated with C_{max}, T_{max}, AUC_{0-24h}, CL/F, half-life, and $AUC_{0-\infty}$ (as data permit). Individual values and descriptive statistics of pevonedistat plasma concentration-time data and PK parameters will be listed and tabulated by treatment/study day. Individual and mean pevonedistat plasma concentration data will also be plotted over time per treatment/study day.

8.3.2 Sampling Schedule (see Appendix X)
Blood samples will be obtained prior to drug administration and at the following time points:

8.3.2.1 All patients

For patients ≥ 10 kg, samples will be obtained at the following time points:
Day 1 of Cycle 1: pre-dose, end of pevonedistat infusion, and at 1, 2, 4, 6-8 and 24 hours post-dose infusion.
Day 8 of Cycle 1: pre-dose, end of pevonedistat infusion, and at 1, 2, 4, 6-8 and 24 hours post-dose infusion.
Day 10 of Cycle 1: pre-dose

For patients < 10 kg, samples will be obtained at the following time points:
Day 1 of Cycle 1: pre-dose; end of infusion; and at 2, 6-8, and 24 hours post-dose infusion.
Day 8 of Cycle 1: pre-dose; end of infusion; and at 2, 6-8, and 24 hours post-dose infusion.
Day 10 of Cycle 1: pre-dose

8.3.3 Sample Collection and Handling Instructions
Blood samples (3 mL) will be collected into a chilled Becton-Dickinson Vacutainer K2 EDTA tube at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug infusion begins and ends.

8.3.4 Sample Processing
- Collect 3.0 mL of venous blood into a chilled K2EDTA lavender top Becton-Dickinson Vacutainer.
- Gently invert the Vacutainer 8 to 10 times to mix the additive with the collected blood prior to centrifugation and place immediately on ice.
- Centrifuge the Vacutainers for 10 minutes at approximately 1100 to 1300 x g (RCF) 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 appropriately labeled 2.0 mL cryogenic vials. 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.
- Cap the labeled storage tubes and freeze the plasma samples immediately at approximately
-70°C or lower. If a -70°C freezer is not available, freeze and store samples at -20°C. No more than 45 minutes will elapse between blood collection and freezing the plasma sample.
- Store samples frozen at approximately -70°C or lower until shipment.

Note: If a -70°C freezer is not available, the samples may be stored at approximately -20°C in a commercial grade freezer with no auto-defrost until

shipment.

8.3.5 Sample Labeling
Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

8.3.6 Sample Shipping Instructions
Samples should be batched per patient and shipped frozen on dry ice in opaque containers at the end of Cycle 1 as per Appendix X-A. Please send an email notification of shipment to the Study-Specific Research Coordinator as well as Matt Dodge at matthew.dodge@covance.com.

8.4 Pharmacodynamics (optional)

8.4.1 Description of Studies
For pharmacodynamic analyses, reverse transcription-polymerase chain reaction (RT-PCR) will be used to analyze the expression of genes regulated following NAE inhibition in whole blood.[1]

In consenting patients ≥ 12 months of age, blood samples (2 mL) will be collected in yellow-top citrate vacutainer tubes at a site distant from the infusion for pharmacodynamic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.4.2 Sampling Schedule (See Appendix XI)

8.4.2.1 Samples will be collected at:

Day 1 of Cycle 1: pre-dose; and at 2, 6-8, and 24 hours post-dose infusion.
Day 8 of Cycle 1: pre-dose; and at 2, 6-8, and 24 hours post-dose infusion.
Day 10 of Cycle 1: pre-dose

8.4.3 Sample Collection and Handling Instructions
Blood samples (2 mL) will be collected in yellow-top citrate vacutainer tubes at a site distant from the infusion for pharmacodynamic evaluation. Record the exact time that the sample is drawn along with the exact time that the drug is administered.

8.4.4 Sample Processing
1. Store at 4ºC until processed.
2. Ship in thermosafe box to address provided in Section 8.4.6.
   - Box should be of thick Styrofoam (NO CLINI-PACS) inside a cardboard box.
   - Pack sample in primary container using soft packing material
   - Place 2 ice packs outside primary container (one ice pack is sufficient Nov-April).
   - Ship overnight mail on Mon-Thurs

8.4.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the PD Study Form (Appendix XI), which must accompany the sample(s).

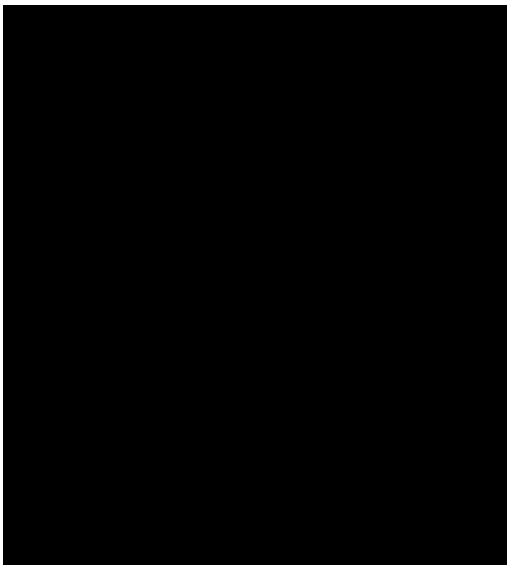
8.4.6 Sample Shipping Instructions

Ship samples to:

[redacted]

9.0 AGENT INFORMATION

9.1 [redacted]



[redacted]

[redacted]

9.1.5 [redacted]

9.1.6 [redacted]

[redacted]

[redacted]

9.1.7 [redacted]

[redacted]

[redacted]

9.1.8 [redacted]

[redacted]

[redacted]

[redacted]

9.1.9 [redacted]

9.1.10 [redacted]

[redacted]

[redacted]

9.1.11 [redacted]

[redacted]

9.1.12 [redacted]

9.1.13 [redacted]

[redacted]

9.1.14 [redacted]

9.2 **CEFIXIME** (11/17/17)
(Suprax®) NSC# NA

9.2.1 Source and Pharmacology

Cefixime is a third-generation cephalosporin antibiotic for oral administration that inhibits bacterial cell wall synthesis by binding to one or more of the penicillin-binding proteins and interfering with the final transpeptidation step of peptidoglycan synthesis. Its spectrum of activity is similar to other third-generation agents, including Enterobacteriaceae, and β-lactamase producing *H. influenzae* and *N. gonorreae*, and *Staph. Aureus.* When taken orally, it is about 40%-50% absorbed whether administered with or without food. The area under the time versus concentration curve is greater by approximately 10%-25% with the oral suspension than with the tablet after doses of 100 to 400 mg, when tested in normal *adult* volunteers. This increased absorption should be taken into consideration if the oral suspension is to be substituted for the tablet. Cefixime serum half-life is approximately 3-4 hours. It is excreted primarily by the kidney. There is no evidence of metabolism of cefixime *in vivo*.

9.2.2 Toxicity

Incidence	Toxicities
Common (>20% of patients)	*None known*
Occasional (4-20% of patients)	• Diarrhea • Nausea • Flatulence • Loose or frequent stools
Rare (≤ 3% of patients)	• Erythema multiforme • Pruritus • Rash maculo-papular • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Urticaria, angioedema • Abdominal pain • Pseudomembranous colitis • Dyspepsia • Transient white blood cell decrease • Neutrophil count decreased • Platelet count decreased • Transient jaundice • Alanine aminotransferase increased • Aspartate aminotransferase increased • Bilirubin increased; anaphylaxis • Allergic reaction • Dizziness • Headache • Seizure • Acute kidney injury • Creatinine increased • Vaginal infection • Vomiting
Pregnancy & Lactation	**Pregnancy Category B** Teratogenic effects were not observed in animal reproduction studies. Cefixime crosses the placenta and can be detected in the amniotic fluid. There are no well-controlled studies of cefixime in pregnant women; effects of cefixime on the fetus are unknown. An increase in most types of birth defects was not found following first trimester exposure to cephalosporins. It is not known whether cefixime is excreted in human milk.

9.2.3 Formulation and Stability

Cefixime is available in scored 400 mg film coated tablets, 400 mg capsules, 100 mg chewable tablets, and 200 mg chewable tablets. The chewable tablets are tutti-frutti flavor and contain aspartame and fd&c red #40 aluminum lake. Cefixime is also available in two strengths as a powder for oral suspension, which when reconstituted, provides either a 100 mg/5 mL or 200 mg/5 mL suspension. The powder for oral suspension is strawberry flavored and contains sodium benzoate,

sucrose, and xanthan gum. After reconstitution, suspension may be stored for 14 days at room temperature or under refrigeration.

Cefixime tablets and powder for oral suspension are stored at 20 - 25°C (68 - 77°F). Do not freeze. The suspension bottle should be kept tightly closed.

9.2.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

Cefixime may be administered with or without food. Administration with food may decrease abdominal distress. Shake the suspension prior to withdrawing dose or administration.

9.2.5 Supplier

Commercially available from various manufacturers. See package insert for further information.

9.3 IRINOTECAN (03/07/17)

[CPT-11,Camptothecin-11,7-ethyl-10-(4-[1-piperidino]-1-piperidino)-carbonyloxy-camptothecin), Camptosar®], NSC #616348

9.3.1 Source and Pharmacology

Irinotecan is a semisynthetic water-soluble analog of camptothecin (a plant alkaloid isolated from *Camptotheca acuminata)*. Irinotecan is a prodrug that requires conversion, by the carboxylesterase enzyme to the topoisomerase-I inhibitor, SN-38 in order to exert anti-tumor activity. SN-38 is approximately 1000 times more potent than irinotecan. Camptothecins interact specifically with the enzyme topoisomerase I which relieves torsional strain in DNA by inducing reversible single-strand breaks. Irinotecan and its active metabolite SN-38 bind to the topoisomerase I-DNA complex and prevent religation of these single-strand breaks. Current research suggests that the cytotoxicity of irinotecan is due to double-strand DNA damage produced during DNA synthesis when replication enzymes interact with the ternary complex formed by topoisomerase I, DNA, and either irinotecan or SN-38. Renal excretion is a minor route of elimination of irinotecan. The majority of the drug is metabolized in the liver. SN-38 is conjugated to glucuronic acid and this metabolite has no anti-tumor activity. The extent of conversion of SN-38 to its glucuronide has been inversely correlated with the risk of severe diarrhea, because the other major route of SN-38 excretion is biliary excretion by canalicular multispecific organic anion transporter (cMOAT) which presumably leads to mucosal injury. In addition, APC and NPC are oxidative metabolites of irinotecan dependent on the CYP3A4 isoenzyme. After intravenous infusion of irinotecan in humans, irinotecan plasma concentrations decline in a multiexponential manner, with a mean terminal elimination half-life of about 6 to 12 hours. The mean terminal elimination half-life of the active metabolite SN-38 is about 10 to 20 hours. Irinotecan is 30% to 68% bound to albumin and SN-38 is approximately 95% bound to albumin.

9.3.2 Toxicity

Incidence	Toxicities
Common (>20% of patients)	• Anemia • Thrombocytopenia • Neutrophil count decreased • White blood cell count decreased • Nausea • Vomiting • Constipation • Anorexia • Fever • Asthenia • Cholinergic symptoms: (rhinitis, increased salivation, miosis, lacrimation, diaphoresis, flushing, and intestinal hyperperistalsis that can cause abdominal cramping and early diarrhea) • Alopecia • Bilirubin increased • Mucositis • Dyspnea • Cough • Weight loss • Pain
Occasional (4-20% of patients)	• Abdominal fullness • Flatulence • Vasodilation • Hypotension • Dehydration • Edema • AST increased • Alkaline phosphatase increased • Ascites • Jaundice • Febrile neutropenia • Infection • Headache • Dizziness • Chills • Insomnia • Rash • Dyspepsia • Somnolence • Thromboembolic events • Pneumonia
Rare (≤ 3% of patients)	• Anaphylaxis • Bradycardia • Disorientation/confusion • Colitis

	• Renal failure (secondary to severe dehydration) • Ileus • Pancreatitis • Pneumonitis (L)
Pregnancy & Lactation	Fetal toxicities and teratogenic effects of irinotecan have been noted in animals at doses similar or less than those used in humans. Toxicities include: decreased skeletal ossification, multiple anomalies, low birth weight and increased fetal mortality. It is not known if irinotecan is excreted into breast milk but it is excreted into rat milk.

(L) Toxicity may also occur later

9.3.3 Formulation & Stability

Each mL of irinotecan injection contains 20 mg irinotecan (on the basis of the trihydrate salt), 45 mg sorbitol, and 0.9 mg lactic acid. When necessary, pH has been adjusted to 3.5 (range, 3.0 to 3.8) with sodium hydroxide or hydrochloric acid. Irinotecan is available in single-dose amber glass vials in 40 mg (2 mL), 100 mg (5 mL), 300 mg (15 mL), and 500 mg (25 mL). Store at controlled room temperature 15°-30°C (59°-86°F). Protect from light. It is recommended that the vial (and backing/plastic blister) should remain in the carton until the time of use.

9.3.4 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

IV Administration: Irinotecan must be diluted prior to infusion. Irinotecan should be diluted in D5W, (preferred) or NS to a final concentration range of 0.12-2.8 mg/mL. The solution is physically and chemically stable for up to 24 hours at room temperature (approximately 25°C) and in ambient fluorescent lighting. Solutions diluted in D5W and stored at refrigerated temperatures (approximately 2°-8°C), and protected from light are physically and chemically stable for 48 hours. Refrigeration of admixtures using NS is not recommended due to a low and sporadic incidence of visible particulates. Care should be taken to avoid extravasation; the use of a central line is suggested.

9.3.5 Supplier

Commercially available from various manufacturers. See package insert for more detailed information.

9.4 TEMOZOLOMIDE - ORAL (06/30/14)

(Temodar®, Temodal®) NSC #362856

9.4.1 Source and Pharmacology

An orally administered alkylating agent, a second generation imidazotetrazine. A prodrug of MTIC, temozolomide spontaneously decomposes to MTIC at physiologic pH. Exerts its effect by cross-linking DNA. This is likely a site-specific alkylation at the O^6-position of guanine with some effect at the N7 position. Temozolomide reaches its peak concentration in 1 hour. Food reduces the rate and extent of absorption. It has an elimination half-life of 1.13 hr (intraperitoneally) and 1.29 hr (orally) with an oral bioavailability of 0.98. Total apparent body clearance is 100 mL/min/m^2 and plasma elimination half-life is ~ 100 minutes.

9.4.2 Toxicity

Incidence	Toxicities
Common (>20% of patients)	• Constipation • Nausea • Vomiting • Diarrhea • Anorexia • Alopecia • Alanine aminotransferase increased • Aspartate aminotransferase increased • Ataxia • Anxiety • Depression • Insomnia • Nervous system disorders – other: hemiparesis or paresis, dizziness, gait disturbance, amnesia, paresthesia, somnolence, headache, seizure, fatigue
Occasional (4-20% of patients)	• Edema limbs • Localized edema • Rash maculopapular • Dysphagia • Mucositis oral • Anemia • Platelet count decreased • White blood cell count decreased • Lymphocyte count decreased • Aplastic anemia • Blood bilirubin increased • Urinary frequency • Cough • Upper respiratory infection • Sinusitis
Rare (≤ 3% of patients)	• Stevens-Johnson syndrome • Toxic epidermal necrolysis • Erythema multiforme • Hypercalcemia

	• Lower gastrointestinal hemorrhage • Upper gastrointestinal hemorrhage • Cholecystitis • Alkaline phosphatase increased • Myelodysplastic syndrome • Leukemia secondary to oncology chemotherapy • Infections and infestations – other: Pneumocystis pneumonia, pulmonary fibrosis, anaphylaxis, allergic reaction, hepatic failure
Pregnancy & Lactation	**Pregnancy Category D** Adequate, well-controlled studies have not been conducted in humans. Women of childbearing potential should be advised against becoming pregnant while taking temozolomide and for at least 6 months following the end of therapy. Temozolomide administration to rats and rabbits at 3/8 and 3/4 the human dose resulted in the development of malformations of the external organs, soft tissues, and skeleton. These animal studies also demonstrated embryolethality (increased resorptions) at similar doses. There is no information available regarding the transmission of temozolomide during lactation; women should avoid breastfeeding while receiving temozolomide.

9.4.3 Formulation and Stability

Temozolomide capsules are available in six different strengths (5, 20, 100, 140, 180, 250 mg). The capsules vary in size, color, and imprint according to strength. In the US, capsules are packaged in 5-count and 14-count bottles. In other countries temozolomide may be packaged in 5-count, 14-count or 20-count bottles. Temozolomide capsules are stored at controlled room temperature.

9.4.4 Guidelines for Administration

See Treatment and Dose Modifications sections of the protocol.

There is a potential for medication errors involving temozolomide capsules resulting in drug overdosages, which may have been caused by dispensing/taking the wrong number of capsules per day and/or product usage exceeding the prescribed dosing schedule.

When dispensing, it is extremely important that prescribing and dispensing include clear instructions on which capsules, and how many of each capsule(s) are to be taken per day. Only dispense what is needed for the course, and clearly indicate how many days of dosing the patient will have and how many days are without temozolomide dosing. When counseling patients, it is important for each patient/parent to understand the number of capsules per day and the number of days that they take temozolomide. It is also important for the patient/parent to understand the number of days that they will be off the medication.

Each strength of temozolomide must be dispensed in a separate vial or in its original container (e.g., bottle or sachet). Based on the dose prescribed, determine the number of each strength of temozolomide capsules needed for the full course as prescribed by the physician. For example, 275 mg/day for 5 days would be dispensed as five 250 mg capsules, five 20 mg capsules, and five 5 mg capsules. Label each container with the appropriate number of capsules to be taken each day. Dispense to the patient/parent, making sure each container lists the strength (mg)

per capsule and that he or she understands to take the appropriate number of capsules of temozolomide from each bottle or vial to equal the total daily dose prescribed by the physician. Institutions that have the capability to dispense temozolomide as daily doses in a blister pack may do so, taking specific precautions to ensure that the appropriate dose is provided and that the patient is educated to understand the daily dosing regimen.

For children unable to swallow the capsules whole, the oral capsules may be formulated into a suspension. To prepare a 10 mg/mL suspension triturate the contents of ten 100 mg capsules (1000 mg), 500 mg povidone K-30 and 25 mg anhydrous citric acid dissolved in 1.5 mL purified water in a glass mortar to form a uniform paste. To the paste add 50 mL of Ora-Plus® by adding a small amount, mixing, and then adding the balance. Transfer to a glass graduated cylinder. Add Ora-Sweet® or Ora-Sweet® SF to a total volume of 100 mL by rinsing the mortar with small amounts of the syrup (Ora-Sweet® or Ora-Sweet® SF). Rinse at least four times. Package in an amber plastic prescription bottle. The packaged suspension is stable for 7 days at room temperature or 60 days in the refrigerator. The suspension should be shaken well before each use. Procedures for proper handling and disposal of cytotoxic drugs should be used when preparing the suspension.[34]

Alternatively, the capsules can be opened and mixed with apple sauce or juice.

9.4.5 Supplier

Commercially available. See package insert for further information.

10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0)
b) Adverse Events requiring removal from protocol therapy (See Section 6.0)
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Completion of 17 cycles of therapy.
f) Physician determines it is not in the patient's best interest.
g) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of pevonedistat (See Section 8.1).
h) Study is terminated by Sponsor.
i) Pregnancy

Patients who are removed from protocol therapy during Cycle 1 should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 30 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Follow-up data will be required unless consent is withdrawn.

10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up
d) Withdrawal of consent for any required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study
f) Patient did not receive protocol treatment after study enrollment

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

Part A1: Patients ≥ 12 months and ≤ 21 years of age:
A minimum of 4 evaluable patients will be required to complete this dose escalation study if 2 subjects experience a dose limiting toxicity (DLT) at Dose Level 1 followed by 2 subjects experiencing a DLT at Dose Level -1. The projected maximum number of evaluable patients is 24 which includes 6 patients at each of Dose Levels 1-3 as well as 6 additional patients for PK analysis. Therefore, the projected maximum number of patients enrolled into this study allowing for 20% inevaluability is 30, and this number is expected to be accrued over 15-30 months. The study design includes several contingencies that may increase the maximum sample size if all contingencies are needed to estimate the MTD. A maximum of 53 patients may be possible in the unlikely scenario that dose levels 1-3 require expansion to 12 patients plus 6 additional patients for steady state analysis and a 20% inevaluable rate. The maximum sample size of 53 patients could accrue over 27-53 months.

Part A2: Patients ≥ 6 months and < 12 months of age:
Patients enrolling on Part A2 of the study will enroll one dose level behind the dose level at which patients in Part A1 are enrolling. Up to 6 evaluable patients may enroll in each lagging dose level. Once the MTD is determined in Part A1, up to 6 evaluable patients may enroll onto the Part A1 MTD. If at any time 2 or more evaluable patients at a lagging dose level experience a DLT, Part A2 will close to further accrual. A maximum of 23 patients is anticipated for Part A2, which accounts for 20% inevaluability rate.

Part A2 will open to enrollment on Dose Level 1 once Part A1 has escalated to Dose Level 2. If the dose level assigned to patients in Part A1 is de-escalated, then patients in Part A2 will continue on treatment at the assigned dose level and new patients will continue to be enrolled at this dose level as well.

Amendment 5 (October 2019)
Amendment 5 will add dose level 4 (35 mg/m2) to the dose escalation part of this study. This amendment will require a minimum of 2 evaluable patients and a maximum of 15 additional patients. The maximum includes 6 patients at dose level 4, 6 additional patients for PK analysis, and 20% inevaluability. The current enrollment rate is approximately 1 patient per month, and this number is expected to be accrued within 15 months. If dose level 4 is expanded to 12 patients due to DLTs of different classes, then the absolute maximum number of patients enrolled is 23. This would require up to 23 months for accrual.

Part A2 is expected to enroll a maximum of 15 patients including 6 at dose level 3, 6 at dose level 4, and 20% inevaluability.

As of 6/30/19, total of 18 patients have been enrolled in Part A1. No patients have enrolled in Part A2. Therefore, the maximum number of patients required to complete this study overall is expected to be 48, and the absolute maximum is 56.

11.2 Definitions

11.2.1 Evaluable For Adverse Events

Any patient who receives at least one dose of the study drug(s) or who experiences

a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-escalation portion during Cycle 1, patients must receive all prescribed doses of pevonedistat and at least 85% of the prescribed dose of irinotecan and temozolomide per protocol guidelines and must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. Patients who do not have DLT and are not considered evaluable for toxicity will be replaced.

11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.5) during Cycle 1 of therapy.

- In the unlikely event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), AND all of the following conditions are met, expansion of the cohort to 12 patients will be considered:

  - One of the DLTs does not appear to be dose-related
  - The Adverse Effects are readily reversible
  - The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

  If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.

- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥ 1/3 of the cohort of patients at the MTD (during the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

11.3 Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study.[35] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled

onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

# Pts Enrolled	# Pts with DLT	# Pts without DLT	# Pts with Data Pending	*Decision*
2	0 or 1	0, 1 or 2	0, 1 or 2	Same dose level
2	2	0	0	De-escalate*
3	0	0, 1 or 2	1, 2 or 3	Same dose level
3	1	0, 1 or 2	0, 1 or 2	Same dose level
3	0	3	0	Escalate**
3	≥ 2	0 or 1	0 or 1	De-escalate*
4	0	0, 1, 2 or 3	1, 2, 3 or 4	Same dose level
4	1	0, 1, 2 or 3	0, 1, 2 or 3	Same dose level
4	0	4	0	Escalate**
4	≥ 2	0, 1 or 2	0, 1 or 2	De-escalate*
5	0	0, 1, 2, 3 or 4	1, 2, 3, 4 or 5	Same dose level
5	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Same dose level
5	0	5	0	Escalate**
5	≥ 2	0, 1, 2 or 3	0, 1, 2 or 3	De-escalate*
6	0	0, 1, 2, 3, or 4	2, 3, 4, 5 or 6	Suspend
6	1	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	Suspend
6	0 or 1	5 or 6	0 or 1	Escalate**
6	≥ 2	0, 1, 2, 3 or 4	0, 1, 2, 3 or 4	De-escalate*

* If six patients already entered at next lower dose level, the MTD has been defined.
** If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule).

In addition to determination of the MTD, a descriptive summary of all toxicities will be reported.

11.4 Inclusion of Children, Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully.

DOMESTIC 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	3	0	0	**3**
Native Hawaiian or Other Pacific Islander	0	0	0	0	**0**
Black or African American	6	3	0	0	**9**
White	16	19	0	0	**35**
More Than One Race	0	3	0	0	**3**
Unknown or not reported	0	3	0	3	**6**
Total	**22**	**31**	**0**	**3**	**56**

11.5 Pharmacokinetic and Pharmacodynamic Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of pevonedistat will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to evaluate the toxicity of pevonedistat, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors, and will be reported descriptively.

All these analyses will be descriptive and exploratory and hypotheses generating in nature.

12.0 EVALUATION CRITERIA

12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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 web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

12.2 Response Criteria for Patients with Solid Tumors

See the table in Section 8.0 for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained on the next consecutive cycle following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[36] Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.2.1 Definitions

12.2.1.1 Evaluable for objective response: Eligible patients who receive at least one dose of protocol therapy will be considered evaluable for response. Evaluable patients who demonstrate a complete or partial response confirmed by central review before receiving non-protocol anti-cancer therapy will be considered a responder. All other evaluable patients will be considered non-responders.

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

12.2.2 Disease Parameters

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

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

12.2.2.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

12.2.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per

organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

12.2.3 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers.

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

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

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

12.2.3.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

12.2.3.4 PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

12.2.3.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

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

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

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

12.2.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

12.2.4.1 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether

target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

12.2.4.2 **Evaluation of Non-Target Lesions**

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

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

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

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

not a single lesion increase.

12.2.5 Overall Response Assessment

Table 2. For Patients with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥ 28 days Confirmation
CR	Non-CR/Non-PD	No	PR	≥ 28 days Confirmation
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥ 28 days from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD**	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 3. For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

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

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

Table 4. Overall Response for Patients with Neuroblastoma and Measurable Disease

CT/MRI	MIBG	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	PD	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	CR/PR/SD	Non-PD	Non-PD	Any	SD
PR	CR/PR	Non-PD	Non-PD	Any	PR
CR/PR	PR	Non-PD	Non-PD	Any	PR
CR	CR	Non-PD	Non-PD	Elevated	PR
CR	CR	CR	CR	Normal	CR

12.2.6 Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.3 Response Criteria for Patients with Solid Tumors and Evaluable Disease

12.3.1 Evaluable Disease
The presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

12.3.2 Complete Response
Disappearance of all evaluable disease.

12.3.3 Partial response
Partial responses cannot be determined in patients with evaluable disease.

12.3.4 Stable Disease (SD)
That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

12.3.5 Progressive Disease
The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression.

12.3.6 Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

12.4.1 MIBG Positive Lesions
Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of ^{123}I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

12.4.2 The following criteria will be used to report MIBG response by the treating institution:

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

12.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy

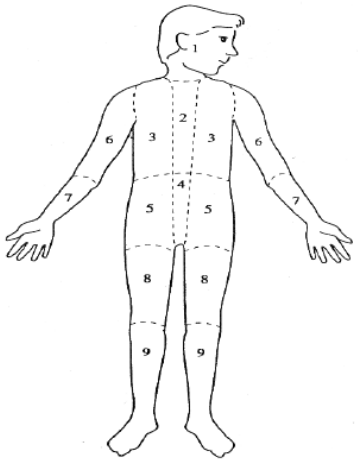
for study endpoint. See Section 8.2.1 for details on transferring images to the Imaging Research Center.

NOTE: This scoring should also be done by the treating institution for end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10th general sector allocated for any extra-osseous lesion visible on MIBG scan**.** In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,
1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:



The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan.

12.4.4 Overall Response Assessment

Table 5. Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only

If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

MIBG	CT/MRI	Bone Scan	Bone Marrow	Catechol	Overall
PD	Any	Any	Any	Any	PD
Any	New Lesion	Any	Any	Any	PD
Any	Any	PD	Any	Any	PD
Any	Any	Any	PD	Any	PD
SD	No New Lesion	Non-PD	Non-PD	Any	SD
PR	No New Lesion	Non-PD	Non-PD	Any	PR
CR	No New Lesion	Non-PD	Non-PD	Elevated	PR
CR	No New Lesion	CR	CR	Normal	CR

12.4.5 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 6 in Section 12.7.

12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

12.5.1 Bone Marrow Involvement

Bone marrow obtained within 28 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by H&E Staining of bilateral bone marrow biopsies and aspirates.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: In patients who enroll with neuroblastoma in bone marrow by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

In patients who enroll without evidence of neuroblastoma in bone marrow will be defined as progressive disease if tumor is detected in 2 consecutive bone marrow biopsies

or aspirations done at least 21 days apart.

Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

12.5.2 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Section 12.7.

12.6 Response Criteria for Patients with CNS Tumors

12.6.1 Measurable Disease

Any lesion that is at minimum 10 mm in one dimension on standard MRI or CT, for CNS tumors.

12.6.2 Evaluable Disease

Evaluable disease is defined as at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers, CSF cytology, or other reliable measures.

12.6.3 Selection of Target and Non-Target Lesions

For most CNS tumors, only one lesion/mass is present and therefore is considered a "target" for measurement/follow up to assess for tumor progression/response. If multiple measurable lesions are present, up to 5 should be selected as "target" lesions. Target lesions should be selected on the basis of size and suitability for accurate repeated measurements. All other lesions will be followed as non-target lesions. The lower size limit of the target lesion(s) should be at least twice the thickness of the slices showing the tumor to decrease the partial volume effect (e.g., 8 mm lesion for a 4 mm slice).

Any change in size of non-target lesions should be noted, though does not need to be measured.

12.6.4 Response Criteria for Target Lesions

Response criteria are assessed based on the product of the longest diameter and its longest perpendicular diameter. Development of new disease or progression in any established lesions is considered progressive disease, regardless of response in other lesions – e.g., when multiple lesions show opposite responses, the progressive disease takes precedence. Response Criteria for target lesions:

- **Complete Response (CR):** Disappearance of all target lesions.
- **Partial response (PR):** ≥ 50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.
- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD.

- **Progressive Disease (PD):** 25% or more increase in the sum of the products of the perpendicular diameters of the target lesions, taking as reference the smallest sum of the products observed since the start of treatment, or the appearance of one or more new lesions.

12.6.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.
- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.
- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

12.6.6 Response criteria for tumor markers (if available):
Tumor markers will be classified simply as being at normal levels or at abnormally high levels.

12.6.7 Overall Response Assessment:
The overall response assessment takes into account response in both target and non-target lesions, the appearance of new lesions and normalization of markers (where applicable), according to the criteria described in the table below. The overall response assessment is shown in the last column, and depends on the assessments of target, non-target, marker and new lesions in the preceding columns.

Target Lesions	**Non-target Lesions**	**Markers**	**New Lesions**	**Overall Response**
CR	CR	Normal	No	**CR**
CR	IR/SD	Normal	No	**PR**
CR	CR, IR/SD	Abnormal	No	**PR**
PR	CR, IR/SD	Any	No	**PR**
SD	CR, IR/SD	Any	No	**SD**
PD	Any	Any	Yes or No	**PD**
Any	PD	Any	Yes or No	**PD**
Any	Any	Any	Yes	**PD**

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.7 from a sequence of overall response assessments.

12.7 Best Response

12.7.1 Evaluation of Best Overall Response

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

Table 6. Sequences of overall response assessments with corresponding best response.

1st Assessment	2nd Assessment	Best Response
Progression		Progressive disease
Stable, PR, CR	Progression	Progressive disease
Stable	Stable	Stable
Stable	PR, CR	Stable
Stable	Not done	Not RECIST classifiable
PR	PR	PR
PR	CR	PR
PR, CR	Not done	Not RECIST classifiable
CR	CR	CR

12.7.2 Duration of Response

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

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

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

13.0 ADVERSE EVENT REPORTING REQUIREMENTS

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. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Step 2: Grade the adverse event using the NCI CTCAE.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

NOTE: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Table A: 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 **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 via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 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 below under the section entitled "Additional Instructions or Exceptions."

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 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 7 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.

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- Any medical event equivalent to CTCAE Grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.

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

Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.

- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

Category	Adverse Events
INVESTIGATIONS	Platelet count decreased
INVESTIGATIONS	White blood cell decreased
INVESTIGATIONS	Neutrophil count decreased
INVESTIGATIONS	Lymphocyte count decreased
BLOOD/LYMPHATICS DISORDERS	Anemia

- Grade 1 and 2 adverse events listed in the table below do not require expedited reporting via CTEPAERS, unless it is associated with hospitalization

Category	Adverse Events
GASTROINTESTINAL DISORDERS	Nausea
GASTROINTESTINAL DISORDERS	Vomiting
GASTROINTESTINAL DISORDERS	Diarrhea
GASTROINTESTINAL DISORDERS	Constipation
GASTROINTESTINAL DISORDERS	Decreased appetite
GASTROINTESTINAL DISORDERS	Abdominal distension
GASTROINTESTINAL DISORDERS	Stomatitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fever
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Peripheral edema
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Fatigue
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	Pain
INFECTIONS AND INFESTATIONS	Infection
INVESTIGATIONS	Alanine aminotransferase increased
INVESTIGATIONS	Aspartate aminotransferase increased
INVESTIGATIONS	Alkaline phosphatase increased
INVESTIGATIONS	GGT increased
INVESTIGATIONS	Blood bilirubin increased
INVESTIGATIONS	Creatinine increased
METABOLISM AND NUTRITION DISODERS	Dehydration
METABOLISM AND NUTRITION	Hypophosphatemia

DISODERS	
MUSCOLOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Myalgia
MUSCOLOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Arthralgia
MUSCOLOSKELETAL AND CONNECTIVE TISSUE DISORDERS	Muscle Spasms
NERVOUS SYSTEM DISORDERS	Dizziness
NERVOUS SYSTEM DISORDERS	Headache
NERVOUS SYSTEM DISORDERS	Peripheral neuropathy
NERVOUS SYSTEM DISORDERS	Paresthesia
PSYCHIATRIC DISORDERS	Anxiety
PSYCHIATRIC DISODERS	Confusion
PSYCHIATRIC DISODERS	Insomnia
RENAL AND URINARY DISODERS	Dysuria
REPIRATORY, THORACIC AND MEDISTINAL DISORDERS	Cough
REPIRATORY, THORACIC AND MEDISTINAL DISORDERS	Nasal congestion
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	Dyspnea
REPIRATORY, THORACIC AND MEDISTINAL DISORDERS	Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Night sweats
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Pruritus
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	Rash

As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (email the ADVL1615 COG study assigned Research Coordinator within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page https://eapps-ctep.nci.nih.gov/ctepaers.

13.3 Expedited Reporting Methods

13.3.1 CTEP-AERS Reporting

To report adverse events in an expedited fashion use the NCI's Adverse Event Expedited Reporting System (CTEP-AERS) that can be found at http://ctep.cancer.gov.

A CTEP-AERS report must be submitted electronically via the CTEP-AERS Web-based application located at https://eapps-ctep.nci.nih.gov/ctepaers/. If prompted to enter a sponsor email address, please type in: PEPCTNAERS@childrensoncologygroup.org.

Send supporting documentation by email to the ADVL1615 COG study assigned Research Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

13.4 Definition of Onset and Resolution of Adverse Events

NOTE: These guidelines below are for reporting adverse events on the COG case report forms and do not alter the guidelines for CTEP-AERS reporting.

13.4.1 If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

13.4.2 If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

13.4.3 The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

13.4.4 The resolution date of the AE is defined as the date at which the AE returns to baseline or less than or equal to Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

13.4.5 An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

13.5 Other Recipients of Adverse Event Reports

13.5.1 Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2) should be reported at the end of each cycle using the forms provided in the CRF packet (see Section 14.1).

13.5.2 COG will forward reports and supporting documentation to the Study Chair, to the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

13.5.3 Adverse events determined to be reportable must also be reported according to the

local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

13.6 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients following their chemotherapy for cancer must be reported via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after protocol treatment for cancer.

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 via CTEP-AERS. Three options are available to describe the event:

1) Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2) Myelodysplastic syndrome (MDS)
3) 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.

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 reporting via CDUS unless otherwise specified.

13.7 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and emailed to the ADVL1615 COG study assigned Research Coordinator along with any additional medical information along with any additional medical information. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

13.7.1 Pregnancy

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as "Pregnancy, puerperium and perinatal conditions - Other (Pregnancy) under the Pregnancy, puerperium and perinatal conditions SOC and reported as Grade 3.

- Pregnancy should be followed until the outcome is known. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is

required.

13.7.2 Pregnancy Loss (Fetal Death)

- Pregnancy loss is defined in CTCAE version 5.0 as "Death in utero."
- Any pregnancy loss should be reported expeditiously, as Grade 4 "Pregnancy loss" under the Pregnancy, puerperium and perinatal conditions SOC. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognized any Grade 5 event as a patient death.

13.7.3 Death Neonatal

- Neonatal death, defined in CTCAE version 5.0 as "Newborn deaths occurring during the first 28 days after birth" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.
- A neonatal death should be reported expeditiously as Grade 4 "Death neonatal" under the "general disorders and administration" SOC when the death is the result of a patient pregnancy or pregnancy in partners of men on study.
- Neonatal death should NOT be reported as "Death neonatal" under the General disorders and administration SOC, a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf.

14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

14.1 Categories of Research Records

Research records for this study can be divided into three categories:

1. Non-computerized Information: Therapy Delivery Maps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.
2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.
3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the case report form (CRF) packet.

See separate CRF Packet, which includes submission schedule.

14.2 CDUS

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP Web site (http://ctep.cancer.gov/reporting/cdus.html).

14.3 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

14.3.1 Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the PEP-CTN scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG PEP-CTN Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

14.3.2 Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the COG PEP-CTN Chair, Vice Chair, and Statistician on a weekly conference call.

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APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

Karnofsky		**Lansky**	
Score	Description	Score	Description
100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
80	Normal activity with effort; some signs or symptoms of disease.	80	Active, but tires more quickly
70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
60	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

APPENDIX II: CORRELATIVE STUDIES GUIDE

Correlative Study	Appx.	Sample Volume			Tube Type
		Volume per sample	Total Volume		
			For subjects ≥ 10 kg	For subjects < 10 kg	
Pharmacokinetics (PK) (required)	X	2 - 3 mL	30 - 45 mL	22 - 33 mL	Vacutainer tubes
Pharmacodynamics (PD)* (optional)	XI	2 mL	18 mL	18 mL	Yellow-top Citrate vacutainer tubes
Total Blood Volume			30 - 63 mL	22 - 51 mL	

*Not applicable for patients < 12 months.

APPENDIX III: TOXICITY-SPECIFIC GRADING

Bilirubin

Grade 1:	> ULN - ≤ 1.5 x ULN
Grade 2:	> 1.5 x ULN- 3.0 x ULN
Grade 3:	> 3.0 x ULN -10.0 x ULN
Grade 4:	> 10.0 x ULN

ALT: For the purpose of this study, the ULN for ALT is 45 U/L regardless of baseline.

Grade 1:	> 45 U/L - ≤ 135 U/L
Grade 2:	136 U/L - 225 U/L
Grade 3:	226 U/L - 900 U/L
Grade 4:	> 900 U/L

AST: For the purpose of this study, the ULN for AST is 50 U/L regardless of baseline.

Grade 1:	> 50 U/L ≤ 150 U/L
Grade 2:	151 U/L -250 U/L
Grade 3:	251 U/L -1000 U/L
Grade 4:	> 1000 U/L

GGT:

Grade 1:	> ULN- 2.5 x ULN
Grade 2:	> 2.5 x ULN - 5.0 x ULN
Grade 3:	> 5.0 x ULN -20.0 x ULN
Grade 4:	> 20.0 x ULN

APPENDIX IV: TEMOZOLOMIDE ORAL CAPSULES DOSING NOMOGRAMS

For the starting dose of 100 mg/m^2/dose:

BSA (m^2)	Total pill count	Calculated dose (mg)	Actual dose (mg)
0.2-0.22*	1	20-22	20
0.23-0.27	2	23-27	25
0.28-0.32	3	28-32	30
0.33-0.37	4	33-37	35
0.38-0.42	2	38-42	40
0.43-0.47	4	43-47	45
0.48-0.52	3	48-52	50
0.53-0.57	5	53-57	55
0.58-0.62	3	58-62	60
0.63-0.67	4	63-67	65
0.68-0.72	5	68-72	70
0.73-0.77	6	73-77	75
0.78-0.82	4	78-82	80
0.83-0.87	5	83-87	85
0.88-0.92	6	88-92	90
0.93-0.97	7	93-97	95
0.98-1.02	1	98-102	100
1.03-1.07	2	103-107	105
1.08-1.12	3	108-112	110
1.13-1.17	4	113-117	115
1.18-1.23	2	118-123	120
1.24-1.28	3	124-128	125
1.29-1.33	4	129-133	130
1.34-1.37	5	134-137	135
1.38-1.42	1	138-142	140
1.43-1.47	2	143-147	145
1.48-1.52	3	148-152	150
1.53-1.57	4	153-157	155
1.58-1.62	2	158-162	160
1.63-1.67	3	163-167	165
1.68-1.72	4	168-172	170
1.73-1.77	5	173-177	175
1.78-1.82	1	178-182	180
1.83-1.87	2	183-187	185
1.88-1.92	3	188-192	190
1.93-1.97	4	193-197	195
1.98-3	2	198-300	200

For the reduced dose of 75 mg/m^2/dose (75% of starting dose):

BSA (m^2)	Total pill count	Calculated dose (mg)	Actual dose (mg)
0.2-0.23	3	15-17.25	15
0.24-0.3	1	18-22.5	20
0.31-0.36	2	23.25-27	25
0.37-0.43	3	27.75-32.25	30
0.44-0.5	4	33-37.5	35
0.51-0.56	2	38.25-42	40
0.57-0.63	3	42.75-47.25	45
0.64-0.7	4	48-52.5	50
0.71-0.76	5	53.25-57	55
0.77-0.83	3	57.75-62.25	60
0.84-0.9	4	63-67.5	65
0.91-0.96	5	68.25-72	70
0.97-1.03	6	72.75-77.25	75
1.04-1.1	4	78-82.5	80
1.11-1.17	5	83.25-87.75	85
1.18-1.23	6	88.5-92.25	90
1.24-1.3	7	93-97.5	95
1.31-1.36	1	98.25-102	100
1.37-1.43	2	102.75-107.25	105
1.44-1.5	3	108-112.5	110
1.51-1.57	4	113.25-117.75	115
1.58-1.64	2	118.5-123	120
1.65-1.7	3	123.75-127.5	125
1.71-1.77	4	128.25-132.75	130
1.78-1.83	5	133.5-137.25	135
1.84-1.9	1	138-142.5	140
1.91-1.97	2	143.25-147.75	145
1.98-3	3	148.5-225	150

APPENDIX V: UNACCEPTABLE ENZYME-INDUCING AND RECOMMENDED NON-ENZYME INDUCING ANTICONVULSANTS

Recommended Non-enzyme inducing anticonvulsants
Generic Name
Clonazepam
Diazepam
Ethosuximide
Ezogabine
Gabapentin
Lacosamide
Lamotrigine
Levetiracetam
Lorazepam
Perampanel
Tiagabine
Topiramate
Valproic Acid
Zonisamide
Unacceptable Enzyme inducing anticonvulsants
Generic Name
Carbamazepine
Felbamate
Phenobarbital
Fosphenytoin
Phenytoin
Primidone
Oxcarbazepine

APPENDIX VI: POTENTIAL DRUG INTERACTIONS

The lists below do not include everything that may interact with chemotherapy. Study Subjects and/or their Parents should be encouraged to talk to their doctors before starting any new medications, using over-the-counter medicines, or herbal supplements and before making a significant change in diet.

Cefixime

Drugs that may interact with cefixime
• **Aminoglycoside antibiotics (such as gentamicin, tobramycin)** • **Oral contraceptives ("birth control")** • **Probenecid** • **Warfarin**
Food and supplements that may interact with cefixime**
• **Thuja**

*** Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Irinotecan

Drugs that may interact with irinotecan

• **Antibiotics**
  ○ **Clarithromycin, erythromycin, nafcillin, rifabutin, rifampin, telithromycin**
• **Antidepressants and antipsychotics**
  ○ **Citalopram, clozapine, desipramine, nefazodone, sertraline**
• **Antifungals**
  ○ **Fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole**
• **Arthritis medications**
  ○ **Leflunomide, tofacitinib**
• **Anti-rejection medications**
  ○ **Cyclosporine, tacrolimus**
• **Antiretrovirals and antivirals**
  ○ **Atazanavir, boceprevir, darunavir, delaviridine, efavirenz, etravirine, fosamprenavir, indinavir, lopinavir, nelfinavir, nevirapine, ritonavir, saquinavir, Stribild, telaprevir, tipranavir**
• **Anti-seizure medications**
  ○ **Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone**
• **Heart medications**
  ○ **Amiodarone, dronedenarone, diltiazem, verapamil**
• **Some chemotherapy (be sure to talk to your doctor about this)**
• **Many other drugs, including the following:**
  ○ **Bosentan, sitaxentan, aprepitant, dexamethasone, ivacaftor, lomitapide, mifepristone, natalizumab, succinylcholine**

Food and supplements that may interact with irinotecan**
• **Echinacea** • **St. John's Wort** • **Some fruits and juices: grapefruit, grapefruit juice, Star fruit**

*** Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

Temozolomide

Drugs that may interact with temozolomide
• Clozapine • Leflunomide • Natalizumab • Tofacitinib
Food and supplements that may interact with temozolomide**
• Echinacea

*** Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

PEVONEDISTAT

Drugs that may interact with pevonedistat

• **Antibiotics**
  ○ **Clarithromycin, rifabutin, rifampin, telithromycin**
• **Antidepressants and antipsychotics**
  ○ **Nefazodone**
• **Antifungals**
  ○ **Itraconazole, ketoconazole, posaconazole, voriconazole**
• **Antiretrovirals and antivirals**
  ○ **Atazanavir, boceprevir, darunavir, indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, Stribild, telaprevir**
• **Anti-seizure medications**
  ○ **Carbamazepine, phenobarbital, phenytoin, primidone**
• **Many other drugs, including the following:**
Enzalutamide, cyclosporine, eltrombopag, gefitinib

Food and supplements that may interact with pevonedistat**
• **St. John's Wort** • **Some fruits and juices: grapefruit, grapefruit juice, Star fruit**

*** Supplements may come in many forms, such as teas, drinks, juices, liquids, drops, capsules, pills, or dried herbs. All forms should be avoided.*

APPENDIX VII: CYP3A4 SUBSTRATES, INDUCERS, AND INHIBITORS

This is NOT an all-inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references.

CYP3A4 substrates	Strong Inhibitors[1]	Moderate Inhibitors	Strong Inducers	Moderate Inducers
alfentanil[4,5] acalabrutinib[5] amiodarone[4] aprepitant/fosaprepitant atorvastatin axitinib bortezomib bosutinib[5] budesonide[5] buspirone[5] cabozantinib calcium channel blockers cisapride citalopram/escitalopram cobimetinib[5] conivaptan[5] copanlisib crizotinib cyclosporine[4] dabrafenib dapsone darifenacin[5] darunavir[5] dasatinib[5] dexamethasone[2] diazepam dihydroergotamine docetaxel doxorubicin dronedarone[5] eletriptan[5] ergotamine[4] erlotinib eplerenone[5] erlotinib estrogens etoposide everolimus[5] fentanyl[4] gefitinib haloperidol ibrutinib[5] idelalisib imatinib indinavir[5] irinotecan isavuconazole[5] itraconazole	atazanavir boceprevir clarithromycin cobicistat darunavir delavirdine grapefruit[3] grapefruit juice[3] idelalisib indinavir itraconazole ketoconazole lopinavir/ritonavir nefazodone nelfinavir posaconazole ritonavir saquinavir telaprevir telithromycin voriconazole	aprepitant conivaptan crizotinib diltiazem dronedarone erythromycin fluconazole fosamprenavir grapefruit[3] grapefruit juice[3] imatinib isavuconazole mifepristone nilotinib verapamil	barbiturates carbamazepine enzalutamide fosphenytoin phenobarbital phenytoin primidone rifampin St. John's wort	bosentan dabrafenib efavirenz etravirine modafinil nafcillin rifapentin

ivacaftor ketoconazole lansoprazole lapatinib losartan lovastatin[5] lurasidone[5] macrolide antibiotics maraviroc[5] medroxyprogesterone methadone midazolam[5] midostaurin[5] modafinil nefazodone nilotinib olaparib ondansetron osimertinib paclitaxel palbociclib pazopanib quetiapine[5] quinidine[4] regorafenib romidepsin saquinavir[5] sildenafil[5] simvastatin[5] sirolimus[4,5] sonidegib sunitinib tacrolimus[4,5] telaprevir tamoxifen temsirolimus teniposide tetracycline tipranavir[5] tolvaptan[5] triazolam[5] trimethoprim vardenafil[5] vemurafenib venetoclax[5] vinca alkaloids zolpidem				

[1] Certain fruits, fruit juices and herbal supplements (star fruit, Seville oranges, pomegranate, gingko, goldenseal) may inhibit CYP 3A4 isozyme, however, the degree of that inhibition is unknown.
[2]Refer to Section 4.2.6.1 regarding use of corticosteroids.
[3]The effect of grapefruit juice (strong vs moderate CYP3A4 inhibition) varies widely among brands and is concentration-, dose-, and preparation-dependent.
[4]Narrow therapeutic range substrates
[5]Sensitive substrates (drugs that demonstrate an increase in AUC of ≥5-fold with strong inhibitors)

APPENDIX VIII: PATIENT INSTRUCTIONS FOR TREAT DIARRHEA

Guidelines for the Treatment of Diarrhea

Institutional practice may be used in place of these guidelines.

You should purchase or will be given a prescription for **loperamide** to have available to begin treatment at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient. Patients will also be instructed to contact their physician if any diarrhea occurs. Patients will be given **loperamide** based on body weight.

Be aware of your child's bowel movements. At the first sign they become softer than usual or if your child has any notable increase in the number of bowel movements over what is normal for him/her, begin taking **loperamide**.

Please follow these directions carefully, using dosing guidelines below:

- Take _____ at the first sign of diarrhea.
- Continue taking _____ every __ hours until the diarrhea slows or the normal pattern of bowel movements returns. Repeat the same doses and frequency if the diarrhea returns.
- Do not exceed _____ in a 24 hour period.
- Please call your doctor if you have any questions about taking loperamide, if your child's diarrhea is not under control after two days, or if he/she is feeling extremely weak, lightheaded, or dizzy.
- Make an extra effort to give your child lots of fluids (several glasses of pedialyte, fruit juices, soda, soup, etc.) while your child is participating in this study.
- Side effects may include tiredness, drowsiness or dizziness. If your child experiences these side effects, or if your child is urinating less frequently than usual, please contact your child's physician.
- Do not give your child any laxatives without consulting with his/her physician.

LOPERAMIDE DOSING RECOMMENDATIONS (NOTE: maximum dose of loperamide for adults is 16 mg/day) *ALL patients: discontinue loperamide when the patient is no longer experiencing significant diarrhea.*	
Weight (kg)	**ACTION**
<13 kg	Take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) after the first loose bowel movement, followed by 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 3 hours. During the night, the patient may take 0.5 mg (2.5 mL [one-half teaspoonful] of the 1 mg/5 mL oral solution) every 4 hours. Do not exceed 4 mg (20 mL or 4 teaspoonfuls) per day.
≥ 13 kg to < 20 kg	Take 1 mg (5 mL [1 teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 4 hours. Do not exceed 6 mg (30 mL or 6 teaspoonfuls) per day.
≥ 20 kg to < 30 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 3 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 8 mg (40 mL or 8 teaspoonfuls) per day.
≥ 30 kg to < 43 kg	Take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) after the first loose bowel movement, followed by 1 mg (5 mL [one teaspoonful] of the 1 mg/5 mL oral solution or one-half tablet) every 2 hours. During the night, the patient may take 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 tablet) every 4 hours. Do not exceed 12 mg (60 mL or 12 teaspoonfuls) per day.
Over 43 kg	Take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) after the first loose bowel movement, followed by 2 mg (10 mL [2 teaspoonfuls] of the 1 mg/5 mL oral solution or 1 capsule or tablet) every 2 hours. During the night, the patient may take 4 mg (20 mL [4 teaspoonfuls] of the 1 mg/5 mL oral solution or 2 capsules or tablets) every 4 hours. Do not exceed 16 mg (80 mL or 16 teaspoonfuls) per day.

APPENDIX IX: NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

The following table presents the New York Heart Association classification of cardiac disease.[37]

Class	Functional Capacity	Objective Assessment
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease

APPENDIX X: PHARMACOKINETICS STUDY FORM

COG Pt ID # _____ Cycle 1, Day 1 Date: _____

Please do not write patient names on this form or on samples.

Patient Weight: _____kg Body Surface Area: _____m^2

Pevonedistat Dose Level: _____mg/m^2 Pevonedistat Total Daily Dose: _____mg

Blood samples (2-3 ml) will be collected in chilled Vacutainer tubes at the following time points (± 10 min): Day 1 (pre-dose, end of infusion, 1 hr, 2 hrs, 4 hrs, 6-8 hrs, and 24 hrs after Day 1 dose); Day 8 (pre-dose, end of infusion, 1 hr, 2 hrs, 4 hrs, 6-8 hrs, and 24 hrs after Day 8 dose); and Day 10 (pre-dose) of Cycle 1.

Record the exact time the sample is drawn along with the exact time pevonedistat is given on Days 1, 8, 15, and 22.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to pevonedistat infusion	___/___/___	|__|__| : |__|__|
Pevonedistat Dose on Day 1 **Date:**___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|	
2	**Day 1**	End of pevonedistat infusion	___/___/___	|__|__| : |__|__|
3*	**Day 1**	1 hr after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
4	**Day 1**	2 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
5*	**Day 1**	4 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
6	**Day 1**	7 (±1) hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
7	**Day 1**	24 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
8	**Day 8**	Prior to pevonedistat infusion	___/___/___	|__|__| : |__|__|
Pevonedistat Dose on Day 8 **Date:**___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|	
9	**Day 8**	End of pevonedistat infusion	___/___/___	|__|__| : |__|__|
10*	**Day 8**	1 hr after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
11	**Day 8**	2 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
12*	**Day 8**	4 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
13	**Day 8**	7 (±1) hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
14	**Day 8**	24 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
15	**Day 10**	Prior to pevonedistat infusion	___/___/___	|__|__| : |__|__|
Pevonedistat Dose on Day 10 **Date:**___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|	

* Collections not required for patients < 10 kg

NOTE: Patients who are removed from therapy during Cycle 1 after receiving the dose on Day 8 should still have the Day 8 sample collected.

One copy of this Pharmacokinetics Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.3.6. See Appendix X-A for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date: _____

(Site personnel responsible for collection of samples)

APPENDIX X-A: GUIDELINES FOR SHIPPING SAMPLES TO COVANCE-MADISON

Regulatory Information

Specific Federal and International Regulations define classes of "Hazardous Materials"1 and "Dangerous Goods"2. Specimens transported to the Covance Madison - Bioanalytical Chemistry Department should be evaluated for their Hazardous Material Class and categorized, packaged, labeled, documented, and transported in accordance with the applicable regulations. Facilities shipping Hazardous Materials are required to maintain designated personnel trained in accordance with part 493 CFR-Subpart H within the last 36 months and International Air Transportation Association (IATA) regulations (if shipping by air) within the last 24 months. The IATA regulation manual also lists additional regulations imposed individually by a variety of Commercial Carriers and Airlines.

The information provided here are Covance Labs guidelines to assist in the proper and safe transport of samples for assay in this facility. They are not to be construed as a replacement or complete summary of applicable DOT (CFR) or IATA regulations.

Guidelines for Packaging Samples

Please organize samples by subject where possible (i.e. box all of subject 001 together, with dividers all of subject 002 together with dividers, etc)

1. Sample container caps should be securely fastened.
    a. Samples should not be transported in glass vials. Samples should be transferred to plastic tubes for transport.
    (If glass must be used, containers must be immobilized. Note: the use of glass greatly increases the risk of breakage and sample loss).
    b. Use labels that will not smear or fall off under cold or moist conditions.

2. Samples should be placed in a primary receptacle (insulated cooler), then into a secondary receptacle (sturdy cardboard box). These primary and secondary containers are available commercially as combination packaging. The package contents are placed in this order:
    a. Wrap the samples in enough absorbent material to absorb at least three times the contents should leakage occur.
    b. Place the wrapped samples in a plastic bag and seal (heat seal or zip lock)
    c. Place the sealed bag in the bottom of the primary receptacle.
    d. Add styrofoam peanuts or equivalent (barrier to dry ice and shock stabilizer)
    e. Add a sheet of cardboard onto the top of the primary receptacle.
    f. If samples are to be frozen, adequate dry ice should be included in the container to last the duration of the journey. (48-72 hrs, at least 7 Kg or 15 pounds, approximately 4 pounds per day of transit).
    g. If there is room remaining, add filler material to avoid content movement during transport.
    h. The primary Styrofoam container should be taped shut and placed in the secondary cardboard container.

3. Complete a sample inventory form. A copy of an example form is attached. If possible please send this electronically (i.e. Excel file) and include all information that would be required in final data tables. **Please indicate sample storage conditions on inventory form.**

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1 Term used by Department of Transportation (DOT) in the Code of Federal Regulations (CFR)
2 Similar term used by the International Air Transportation Association (IATA), will use the term Hazardous Material in this document
3 Part 49 is "Hazardous Materials in Commerce" in the CFR

4. Seal the sample inventory form(s) into a protected plastic bag. Place the plastic bag containing the sample inventory form(s) on top of the secured styrofoam primary container lid so that it is immediately accessible upon opening the box.

5. Tape the shipping box securely closed. Use tape that is resistant to moisture and cold.

6. Place Biohazard warnings on outside of box (if applicable).

7. Label the box exterior in accordance with the applicable DOT CFR / IATA Regulations.

8. Complete an address label and attach it to the outside of the box.

****

Guidelines for Shipping Samples

Send samples to:

For Shipments:
Mohammad Koupaei, PhD
Covance Bioanalytical Laboratory Services Inc.
3301 Kinsman Boulevard
Madison, WI 53704-2523
Attn: Sample Management—Bioanalytical (Rm131D 1S)

1. Samples should be shipped **least 2 days prior to a USA National Holiday.**

2. Frozen samples should not be shipped after Wednesday **(samples should arrive at Covance by Friday, not on Saturday or Sunday)**

3. Call the Covance Bioanalytical Services Sample Management department **on the day prior to shipment (1-888-541-7377 Ext 2540, Ext 2187, or Ext 2327),** as notification of the intended shipment, ***OR*** e-mail Madison.SA@Covance.com with shipment information (tracking numbers and number of boxes sent).

4. **Samples to be shipped to the United States from outside the U.S.A.**, should be shipped using an International carrier. The name of the carrier, shipping date, expected date of arrival, and tracking numbers should be e-mailed to Madison.SA@Covance.com and mohammad.koupaei@covance.com and matthew.dodge@covance.com with a copy to the study-specific Research Coordinator, prior to shipment.

5. Any questions regarding shipping instructions may be directed to the Sample Management Group at 1-888-541-7377 Ext 2540, Ext 2187, or Ext 2327, or via Fax 608-245-7082. International phone code is 001.

APPENDIX XI: PHARMACODYNAMICS STUDY FORM

COG Pt ID # _____ Cycle 1, Day 1 Date: _____
Please do not write patient names on this form or on samples.

Patient Weight: _____kg Body Surface Area: _____m^2

Pevonedistat Dose Level: _____mg/m^2 Pevonedistat Total Daily Dose: _____mg

Blood samples (2-3 ml) will be collected in yellow-top Citrate vacutainer tubes at the following time points (± 10 min): Day 1 (pre-dose, 2 hrs, 4 hrs, 6-8 hrs, and 24 hrs after Day 1 dose); Day 8 (pre-dose,, 2 hrs, 4 hrs, 6-8 hrs, and 24 hrs after Day 8 dose); and Day 10 (pre-dose) of Cycle 1.

Record the exact time the sample is drawn along with the exact time pevonedistat is given on Days 1, 8, 15, and 22.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to pevonedistat infusion	___/___/___	|__|__| : |__|__|
Pevonedistat Dose on Day 1 **Date:**___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Start Time:** |__|__| : |__|__|	
2	**Day 1**	2 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
3	**Day 1**	7 (±1) hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
4	**Day 1**	24 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
5	**Day 8**	Prior to pevonedistat infusion	___/___/___	|__|__| : |__|__|
Pevonedistat Dose on Day 8 **Date:**___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|	
6	**Day 8**	2 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
7	**Day 8**	7 (±1) hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
8	**Day 8**	24 hrs after end of pevonedistat infusion	___/___/___	|__|__| : |__|__|
9	**Day 10**	Prior to pevonedistat infusion	___/___/___	|__|__| : |__|__|
Pevonedistat Dose on Day 10 **Date:**___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|	

* Collections not required for patients < 10 kg

NOTE: Patients who are removed from therapy during Cycle 1 after receiving the dose on Day 8 should still have the Day 8 sample collected.

One copy of this Pharmacodynamics Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.4.6. See Section 8.4 for detailed guidelines for packaging and shipping PD samples.

Signature: _____ Date: _____
(Site personnel responsible for collection of samples)

APPENDIX XII: BLOOD PRESSURE LEVELS FOR CHILDREN BY AGE AND HEIGHT PERCENTILE

Blood pressure (BP) levels for <u>BOYS</u>

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	99th	105	106	108	110	112	113	114	61	62	63	64	65	66	66
2	99th	109	110	111	113	115	117	117	66	67	68	69	70	71	71
3	99th	111	112	114	116	118	119	120	71	71	72	73	74	75	75
4	99th	113	114	116	118	120	121	122	74	75	76	77	78	78	79
5	99th	115	116	118	120	121	123	123	77	78	79	80	81	81	82
6	99th	116	117	119	121	123	124	125	80	80	81	82	83	84	84
7	99th	117	118	120	122	124	125	126	82	82	83	84	85	86	86
8	99th	119	120	122	123	125	127	127	83	84	85	86	87	87	88
9	99th	120	121	123	125	127	128	129	84	85	86	87	88	88	89
10	99th	122	123	125	127	128	130	130	85	86	86	88	88	89	90
11	99th	124	125	127	129	130	132	132	86	86	87	88	89	90	90
12	99th	126	127	129	131	133	134	135	86	87	88	89	90	90	91
13	99th	128	130	131	133	135	136	137	87	87	88	89	90	91	91
14	99th	131	132	134	136	138	139	140	87	88	89	90	91	92	92
15	99th	134	135	136	138	140	142	142	88	89	90	91	92	93	93
16	99th	136	137	139	141	143	144	145	90	90	91	92	93	94	94
≥17	99th	139	140	141	143	145	146	147	92	93	93	94	95	96	97

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" <u>PEDIATRICS</u> Vol. 114 No. 2 August 2004, pp. 555-576.

Blood pressure (BP) levels for GIRLS

		Systolic Blood Pressure, mm Hg							Diastolic Blood Pressure, mm Hg						
Age	BP	Percentile of Height							Percentile of Height						
(years)	Percentile	5th	10th	25th	50th	75th	90th	95th	5th	10th	25th	50th	75th	90th	95th
1	99th	108	108	109	111	112	113	114	64	64	65	65	66	67	67
2	99th	109	110	111	112	114	115	116	69	69	70	70	71	72	72
3	99th	111	111	113	114	115	116	117	73	73	74	74	75	76	76
4	99th	112	113	114	115	117	118	119	76	76	76	77	78	79	79
5	99th	114	114	116	117	118	120	120	78	78	79	79	80	81	81
6	99th	115	116	117	119	120	121	122	80	80	80	81	82	83	83
7	99th	117	118	119	120	122	123	124	81	81	82	82	83	84	84
8	99th	119	120	121	122	123	125	125	82	82	83	83	84	85	86
9	99th	121	121	123	124	125	127	127	83	83	84	84	85	86	87
10	99th	123	123	125	126	127	129	129	84	84	85	86	86	87	88
11	99th	125	125	126	128	129	130	131	85	85	86	87	87	88	89
12	99th	127	127	128	130	131	132	133	86	86	87	88	88	89	90
13	99th	128	129	130	132	133	134	135	87	87	88	89	89	90	91
14	99th	130	131	132	133	135	136	136	88	88	89	90	90	91	92
15	99th	131	132	133	134	136	137	138	89	89	90	91	91	92	93
16	99th	132	133	134	135	137	138	139	90	90	90	91	92	93	93
≥17	99th	133	133	134	136	137	138	139	90	90	91	91	92	93	93

Instructions for using this BP Chart:

1. Measure the patient's blood pressure using an appropriate size cuff.
2. Select appropriate chart for a female or male patient.
3. Using the "age" row and "height" column determine if the BP is within the ULN.

This table was taken from "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" PEDIATRICS Vol. 114 No. 2 August 2004, pp. 555-576.

APPENDIX XIII-A: THERAPY DELIVERY MAPS (TDMS) FOR CYCLE 1

Therapy Delivery Map – Cycle 1

This Therapy Delivery Map (TDM) relates to Cycle 1. Cycle 1 lasts 28 days. This TDM can be used for all dose levels of pevonedistat. Please record the dose level below. This TDM is intended to serve as a tool to assist in scheduling the required observations for the study; the schedule indicated in the chart below should be considered an example. The actual schedule must comply with the timing of required observations per Section 8 of the protocol.
This form is to be completed and uploaded into RAVE at the end of every cycle.

_____ Accession #

_____ Patient COG ID number

_____ Institution

Criteria to start each cycle are listed in Section 5.3. Extensive treatment details are in Section 5.1. This TDM is on 2 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Pevonedistat IND # 136078	IV over 60 minutes	Dose Level -1: 10 mg/m^2 Dose Level 1: 15 mg/m^2 Dose Level 2: 20 mg/m^2 Dose Level 3: 25 mg/m^2 Dose Level 4: 35 mg/m^2	1, 8, 10, 12	Administer alone on Day 1. Administer immediately after irinotecan on Days 8, 10, and 12. The dose level will be assigned via OPEN at the time of study enrollment.
Cefixime	PO	8 mg/kg/dose daily	6-15, 27-28	Maximum dose is 400 mg/day.
Temozolomide (TEMO)	PO	100 mg/m^2/dose daily	8-12	Maximum dose is 200 mg/day. See Appendix IV for oral capsules dosing nomogram.
Irinotecan (IRIN)	IV over 90 minutes	- **If BSA < 0.6 m^2:** BSA-based dosing (See Section 5.1 dosing table) - **If BSA ≥ 0.6 m^2:** 50 mg/m^2/dose daily	8-12	Administer one hour after temozolomide.

NOTE: PCP prophylaxis should start on Cycle 1 Day 8, given twice daily for 3 consecutive days a week (i.e., BID Friday, Saturday, Sunday), every week or per institutional practice, until the end of protocol therapy. See Section 5.1 for details.

Assigned Dose Level _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	**Pevonedistat** _____ mg	**TEMO** _____ mg	**IRIN** _____ mg	**Cefixime** _____ mg	Studies
		PRE					a - m, n*, o, p
		1	_____ mg				h, m, n*
		…					
		4					e
		5					
		6				_____ mg	
		7				_____ mg	
		8	_____ mg	_____ mg	_____ mg	_____ mg	b, e - h, m, n*
		9		_____ mg	_____ mg	_____ mg	
		10	_____ mg	_____ mg	_____ mg	_____ mg	h, m, n*
		11		_____ mg	_____ mg	_____ mg	
		12	_____ mg	_____ mg	_____ mg	_____ mg	e, h
		13				_____ mg	
		14				_____ mg	
		15				_____ mg	b, e - h
		…					
		19					e
		…					
		22					b, e - h
		…					
		26/-1					e
		27/0				_____ mg	
		28/1				_____ mg	a - h, j - k, l^, p
			Following completion of Cycle 1, Cycle 2 starts on Day 28 or when starting criteria are met (see Section 5.3), whichever occurs later.				

* For consenting patients only.
^ Study may be obtained within 72 hours prior to the start of the subsequent cycle.

See Section 6.0 for Dose Modifications for Adverse Events and Section 7.0 and the COG Member website for Supportive Care Guidelines.

Cycle 1

Cycle 1

Required Observations in Cycle 1

All baseline studies must be performed within 7 days prior to enrollment unless otherwise indicated below. See Section 8.0 for schedule of assessments.

a. History
b. Physical exam with vital signs: Vital signs should be checked prior to each pevonedistat infusion. Vital signs will be also be assessed at the end of treatment.
c. Height, weight, BSA
d. Performance status
e. CBC, differential, platelets: Twice weekly during Cycle 1. If patients have Grade 4 neutropenia or thrombocytopenia, CBCs should be checked at least every other day until recovery to Grade 3 or until the criteria for dose limiting toxicity are met.
f. Electrolytes including Ca^{++}, PO_4, MG^{++}
g. Creatinine
h. ALT, AST, bilirubin: Check prior to each dose of pevonedistat, then weekly for remaining weeks of cycle. If patients have Grade 2, 3, or 4 ALT/AST/bilirubin on or after Cycle 1 Day 8, AST/ALT/bilirubin should be checked at least every other day until recovery to ≤ Grade 1. See Section 6.2.4 for more details.
i. ECHO/EKG
j. Albumin, Pulse Oximetry
k. Pregnancy test: Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable methods of birth control. All women of childbearing potential must have a pregnancy test done every cycle prior to initiation of a new cycle.
l. Tumor disease evaluation: Tumor disease evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.
m. Pharmacokinetics (required): See Section 8.3 for details.
n. Pharmacodynamics (optional): See Section 8.4 for details.
o. INR
p. Bone marrow evaluation. If a solid tumor patient is suspected to have or has a history of bone marrow involvement then a pre-study bone marrow biopsy and/or aspirate is required. This should then be repeated with each tumor disease evaluation if pre-study bone marrow was positive for metastatic disease.

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

APPENDIX XIII-B: THERAPY DELIVERY MAPS (TDMS) FOR ALL SUBSEQUENT CYCLES

Therapy Delivery Map – All Subsequent Cycles This Therapy Delivery Map (TDM) relates to all subsequent cycles (Cycles 2+). Each cycle lasts 21 days. This TDM can be used for all dose levels of pevonedistat. Please record the dose level in the chart below. Treatment may continue in the absence of disease progression or unacceptable toxicity. A cycle may be repeated 17 times, up to a total duration of therapy of 12 months. Use a copy of this page once for each cycle (please note cycle number below). This form is to be completed and uploaded into RAVE at the end of every cycle.	_____ Accession # _____ Patient COG ID number _____ Institution

Criteria to start each cycle are listed in Section 5.3. Extensive treatment details are in Section 5.1. This TDM is on 3 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
Cefixime	PO	8 mg/kg/dose daily	-1 to 8, 20-21	Maximum dose is 400 mg/day.
Temozolomide (TEMO)	PO	100 mg/m^2/dose daily	1-5	Maximum dose is 200 mg/day. See Appendix IV for oral capsules dosing nomogram.
Irinotecan (IRIN)	IV over 90 minutes	- **If BSA < 0.6 m^2:** BSA-based dosing (See Section 5.1 dosing table) - **If BSA ≥ 0.6 m^2:** 50 mg/m^2/dose daily	1-5	Administer one hour after temozolomide.
Pevonedistat IND # 136078	IV over 60 minutes	Dose Level -1: 10 mg/m^2 Dose Level 1: 15 mg/m^2 Dose Level 2: 20 mg/m^2 Dose Level 3: 25 mg/m^2 Dose Level 4: 35 mg/m^2	1, 3, 5	Administer immediately after irinotecan. If pevonedistat is delayed, a minimum of 1 calendar day between any 2 doses should be maintained. A maximum of 3 doses of pevonedistat per Cycles 2+ should not be exceeded.

NOTE: PCP prophylaxis should start on Cycle 1 Day 8, given twice daily for 3 consecutive days a week (i.e., BID Friday, Saturday, Sunday), every week or per institutional practice, until the end of protocol therapy. See Section 5.1 for details.

Cycle # _____ Assigned Dose Level _____ Ht _____cm Wt _____kg BSA _____m^2

Date Due	Date Given	Day	Pevonedistat _____ mg	TEMO _____ mg	IRIN _____ mg	Cefixime _____ mg	Studies
			Enter calculated dose above and actual dose administered below				
		-1*				_____ mg*	
		0*				_____ mg*	a - d, h, j - k
		1	_____ mg	_____ mg	_____ mg	_____ mg	
		2		_____ mg	_____ mg	_____ mg	
		3	_____ mg	_____ mg	_____ mg	_____ mg	h
		4		_____ mg	_____ mg	_____ mg	
		5	_____ mg	_____ mg	_____ mg	_____ mg	h
		6				_____ mg	
		7				_____ mg	
		8				_____ mg	e – g, h
		…					
		15					e – g, h
		…					
		19/-1					
		20/0				_____ mg	
		21/1				_____ mg	a - d, h, j - k, l#, p
			Following completion of this cycle, the next cycle will start on Day 21 or when starting criteria are met (see Section 5.3), whichever occurs later.				

End of Cycle 2, then every other cycle x 2 then q 3 cycles *Cefixime on these days should be reported as the last two days of the previous cycle.

See Section 5.0 for Dose Modifications for Adverse Events and Section 7.0 and the COG Member website for Supportive Care Guidelines.

All Subsequent Cycles

Required Observations in All Subsequent Cycles

All baseline studies must be performed within 7 days prior to enrollment unless otherwise indicated below. See Section 8.0 for schedule of assessments.

a. History^
b. Physical exam with vital signs^: Vital signs should be checked prior to each pevonedistat infusion. Vital signs will also be assessed at the end of treatment.
c. Height, weight, BSA^
d. Performance status^
e. CBC, differential, platelets: If patients develop Grade 4 neutropenia, CBCs should be checked every 3 to 4 days until recovery to Grade 3. If patients remain on study for > 4 cycles and ≥ 4 cycles and ≥ Grade 3 cytopenias are not observed, then CBCs may be obtained at the start of subsequent cycles and as clinically indicated.
f. Electrolytes including Ca++, PO4, MG++^
g. Creatinine^
h. ALT, AST, bilirubin*: Check prior to each dose of pevonedistat, then weekly for remaining weeks of cycle. If patients have Grade 2, 3, or 4 ALT/AST/bilirubin on or after Cycle 1 Day 8, AST/ALT/bilirubin should be checked at least every other day until recovery to ≤ Grade 1. See Section 6.2.4 for more details.
i. ECHO/EKG
j. Albumin^; Pulse Oximetry
k. Pregnancy test^: Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable methods of birth control. All women of childbearing potential must have a pregnancy test done every cycle prior to initiation of a new cycle.
l. Tumor disease evaluation[5]: Tumor disease evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. If the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.
m. Pharmacokinetics (required): See Section 8.3 for details.
n. Pharmacodynamics (optional): See Section 8.4 for details.
o. INR
p. Bone marrow evaluation. With tumor disease evaluation; end of cycle 2, then every other cycle x2, then every 3 cycles. If a solid tumor patient is suspected to have or has a history of bone marrow involvement then a pre-study bone marrow biopsy and/or aspirate is required. This should then be repeated with each tumor disease evaluation if pre-study bone marrow was positive for metastatic disease.

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

This listing only includes evaluations necessary to answer the primary and secondary aims. OBTAIN OTHER STUDIES AS REQUIRED FOR GOOD CLINICAL CARE.

Comments
(Include any held doses, or dose modifications)

All Subsequent Cycles