CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

NCI Pediatric Early Phase Clinical Trials Network

A program funded by the National Cancer Institute of the National Institutes of Health

Pediatric Early Phase Clinical Trial Network (PEP-CTN) and Developmental Therapeutics (DVL) Chair
Brenda J. Weigel, M.D.
weige007@umn.edu

PEP-CTN and Developmental Therapeutics (DVL) Vice Chair
Elizabeth Fox, M.D.
elizabeth.fox@stjude.org

PEP-CTN Operations Data & Statistics Center Director
Thalia Beeles, MPH
tbeeles@childrensoncologygroup.org

PEP-CTN Statistician
Charles G. Minard, Ph.D.
minard@bcm.edu

PEP-CTN and DVL Chair's Office
University of Minnesota/
Masonic Cancer Center
Masonic Children's Hospital
420 Delaware Street, SE
MMC 366
Minneapolis, MN 55455

P 612 626 5501
F 612 624 3913

Children's Oncology Group Group Chair
Douglas S. Hawkins, MD
Seattle Children's Research Institute
Mailstop: JMB 9
1900 9th Avenue
Seattle, WA 98101
P 206 884 1107
doug.hawkins@seattlechildrens.org

PEP-CTN Operations Data & Statistics Center
800 Royal Oaks Drive
Suite 210
Monrovia, CA 91016

P 626 241 1500
F 626 445 4334

A National Cancer Institute-supported member group of the National Clinical Trials Network

August 27, 2020

Martha Kruhm, M.S., RAC
Head, Protocol and Information Office (PIO)
National Institutes of Health/NCI/DCTD/CTEP/OIB/PIO
9609 Medical Center Drive, OIB MSC 9742, Room #5W246
Bethesda, MD 20892-9742

Dear Ms. Kruhm,

Enclosed please find Amendment #3A to **ADVL1712**, *A Feasibility Trial of MLN4924 (pevonedistat, TAK 924) given in Combination with Azacitidine, Fludarabine, and Cytarabine, in Children, Adolescents, and Young Adults with Relapsed or Refractory Acute Myeloid Leukemia or Myelodysplastic Syndrome.*

This amendment is being submitted in response to a Request for Rapid Amendment (RRA) from Dr. John J. Wright (wrightj@ctep.nci.nih.gov), dated August 7, 2020. In this amendment, the revised CAEPR for MLN4924 (Pevonedistat HCl) (Version 2.3, July 10, 2020) has been inserted in the protocol, and the associated risk information in the informed consent document has been revised. All revisions are detailed in the summary of changes below.

Please let me know if you have any questions or need additional information.

Sincerely,
Jennifer Knothe, Protocol Coordinator (for)
Katherine Tarlock, M.D., ADVL1712 Study Chair, and
Brenda Weigel, M.D., PI, PEP-CTN

SUMMARY OF CHANGES: PROTOCOL

In accordance with the above discussion, the following specific revisions have been made to the protocol. Additions are in **boldfaced** font and deletions in ~~strikethrough~~ font.

#	Section	Page(s)	Change
1.	General	Throughout	Updated protocol version date in the footer.
2.	Cover Page	1	Updated version date and amendment number.

3.	9.1.10	40-43	Inserted revised CAEPR for MLN4924 (Pevonedistat HCl) (Version 2.3, July 10, 2020).
			
			Specific changes are as follows:
			
			• Added New Risk:
			  • Also Reported on MLN4924 Trials But With Insufficient Evidence for Attribution: Ascites; Hypertension; Non-cardiac chest pain; Treatment related secondary malignancy; Urinary retention; White blood cell decreased
			
			• Increase in Risk Attribution:
			  • Changed to Less Likely from Also Reported on MLN4924 Trials But With Insufficient Evidence for Attribution: Urinary tract infection
			
			• Decrease in Risk Attribution:
			  ○ Changed to Less Likely from Likely: Constipation; Dizziness
			  ○ Changed to Also Reported on MLN4924 Trials But With Insufficient Evidence for Attribution from Less Likely: Rash maculo-papular

Activated: 05/01/19
Closed:

Version Date: 08/27/20
Amendment # 3A

CHILDREN'S ONCOLOGY GROUP

ADVL1712

A FEASIBILITY TRIAL OF MLN4924 (PEVONEDISTAT, TAK 924) GIVEN IN COMBINATION WITH AZACITIDINE, FLUDARABINE, AND CYTARABINE, IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH RELAPSED OR REFRACTORY ACUTE MYELOID LEUKEMIA OR MYELODYSPLASTIC SYNDROME

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

THIS PROTOCOL IS FOR RESEARCH PURPOSES ONLY, AND SHOULD NOT BE COPIED, REDISTRIBUTED OR USED FOR ANY OTHER PURPOSE. MEDICAL AND SCIENTIFIC INFORMATION CONTAINED WITHIN THIS PROTOCOL IS NOT INCLUDED TO AUTHORIZE OR FACILITATE THE PRACTICE OF MEDICINE BY ANY PERSON OR ENTITY. *RESEARCH* MEANS A SYSTEMATIC INVESTIGATION, INCLUDING RESEARCH DEVELOPMENT, TESTING AND EVALUATION, DESIGNED TO DEVELOP OR CONTRIBUTE TO GENERALIZABLE KNOWLEDGE. THIS PROTOCOL IS THE RESEARCH PLAN DEVELOPED BY THE CHILDREN'S ONCOLOGY GROUP TO INVESTIGATE A PARTICULAR STUDY QUESTION OR SET OF STUDY QUESTIONS AND SHOULD NOT BE USED TO DIRECT THE PRACTICE OF MEDICINE BY ANY PERSON OR TO PROVIDE INDIVIDUALIZED MEDICAL CARE, TREATMENT, OR ADVICE TO ANY PATIENT OR STUDY SUBJECT. THE PROCEDURES IN THIS PROTOCOL ARE INTENDED ONLY FOR USE BY CLINICAL ONCOLOGISTS IN CAREFULLY STRUCTURED SETTINGS, AND MAY NOT PROVE TO BE MORE EFFECTIVE THAN STANDARD TREATMENT. *ANY PERSON WHO REQUIRES MEDICAL CARE IS URGED TO CONSULT WITH HIS OR HER PERSONAL PHYSICIAN OR TREATING PHYSICIAN OR VISIT THE NEAREST LOCAL HOSPITAL OR HEALTHCARE INSTITUTION.*

STUDY CHAIR

Katherine Tarlock, MD
Seattle Children's Hospital
4800 Sand Point Way NE
Seattle, WA 98105
Phone: (206) 987-2106
Fax: (206) 987-3946
Email: katherine.tarlock@seattlechildrens.org

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

TABLE OF CONTENTS

STUDY COMMITTEE

STUDY CHAIR
Katherine Tarlock, MD
Seattle Children's Hospital
4800 Sand Point Way NE
Seattle, WA 98105
Phone: (206) 987-2106
Fax: (206) 987-3946
e-mail: katherine.tarlock@seattlechildrens.org

Elizabeth Fox, MD
Vice Chair, Developmental Therapeutics
Saint Jude Children's Research Hospital
262 Danny Thomas Place
Memphis, TN 38105
Phone: (901) 595-3300
Fax: (901) 595-7031
Email: elizabeth.fox@stjude.org

STUDY VICE CHAIR
Todd Cooper, DO
Seattle Children's Hospital
4800 Sand Point Way NE
Seattle, WA 98105
Phone: (206) 987-2106
Fax: (206) 987-3946
e-mail: todd.cooper@seattlechildrens.org

STUDY PHARMACIST
Sarah Menig, PharmD
Seattle Children's Hospital
4800 Sand Point Way NE
Seattle, WA 98105
Phone: (206) 987-2033
Fax: (206) 987-5058
E-mail: sarah.menig@seattlechildrens.org

SENIOR STATISTICIAN
Charles Minard, PhD
Baylor College of Medicine
One Baylor Plaza, BCM 122
Houston, TX 77030
Phone: (713) 798-2353
Fax: (713) 798-2813
Email: minard@bcm.edu

STUDY NURSE
Sharon Bergeron, RN, BSN, CPON
Children's Hospital of Orange County
1201 West La Veta
Orange, CA 92868
Phone: (714) 509-4396
Fax: (714) 509-4365
E-mail: sbergeron@choc.org

STUDY COMMITTEE MEMBERS
Brenda J. Weigel, MD
Chair, Developmental Therapeutics
Hematology/Oncology
University of Minnesota Medical Center - Fairview
Department of Pediatrics
420 Delaware Street, SE MMC 366
Minneapolis, MN 55455
Phone: (612) 626-5501
Fax: (612) 624-3913
E-mail: weige007@umn.edu

STUDY CRA
CRA NAME
Address
Address
Address
Address
Phone:
Fax:
E-mail:

STUDY COMMITTEE, CONT.

COG OPERATIONS STAFF

PROTOCOL COORDINATOR
Alina Stout, BS
Children's Oncology Group – Operations Center
Phone: (626) 241-1566
Fax: (626) 445-4334
E-mail: astout@childrensoncologygroup.org

MASTER STATISTICIAN
Xiaowei Liu, MS
Children's Oncology Group – Operations Center
Phone: (626) 241-1535
Fax: (626) 445-4334
E-mail: xwliu@childrensoncologygroup.org

RESEARCH COORDINATOR
Ashley Rodela, BS
Phone: (626) 241-1624
Fax: (626) 445-4334
E-mail: arodela@childrensoncologygroup.org

AGENT NSC# AND IND#'s
Agent Supplied by CTEP:
MLN4924 (NSC#793435)

Commercial Agents:
Azacitidine (Vidaza®, NSC#102816)
Cytarabine (Cytosar®, NSC#63878)
Fludarabine (Fludara®, NSC#103805)
Hydrocortisone (Solu-cortef®, NSC#10483)
Methotrexate (Trexall®, NSC#740)

IND Sponsor: DCTD, NCI

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

SEE SECTION 8.2.6, 8.3.6 AND 8.4.6 FOR SPECIMEN SHIPPING ADDRESSES

This trial is covered by a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

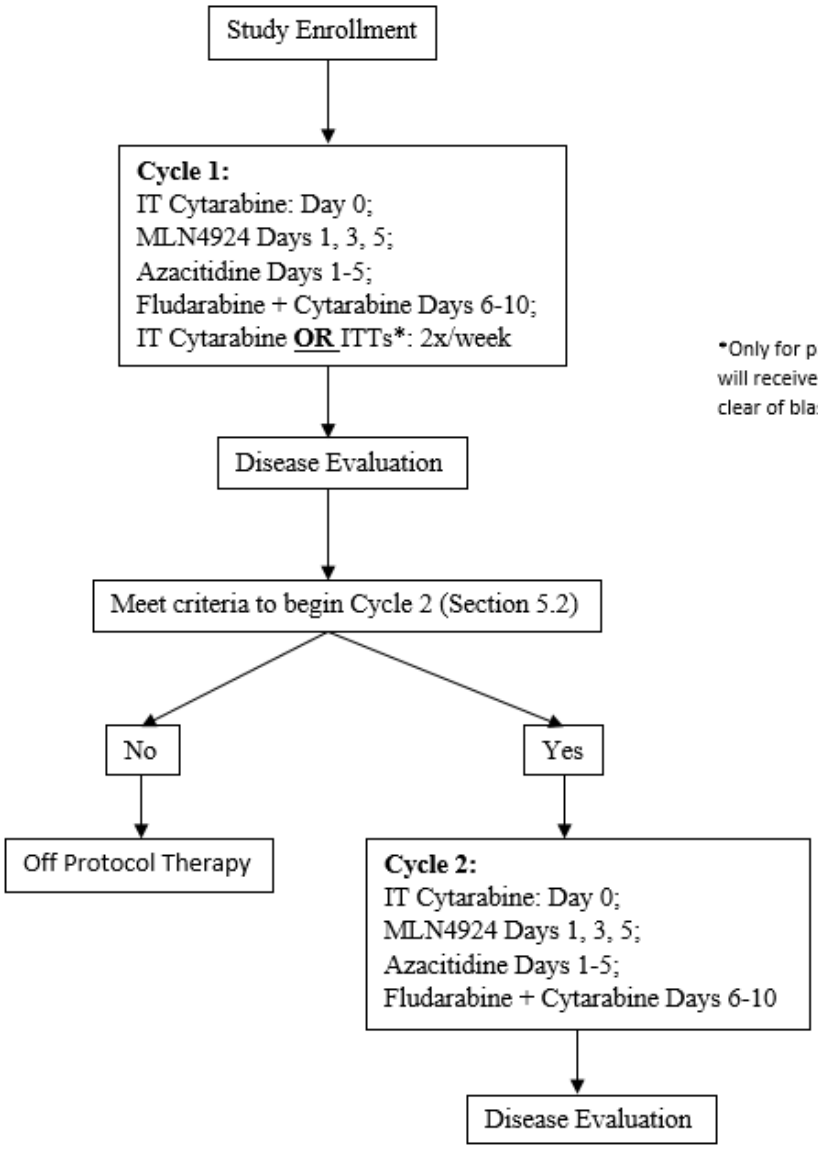
The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

ABSTRACT

Outcomes for children with relapsed AML remain poor and have not significantly improved over the past decade. For patients who do experience relapse, effective combination therapies that achieve complete remission so that patients can proceed to stem cell transplant remain the only chance for long-term survival. Thus, new therapies are urgently needed and as single agents are inadequate in patients with relapsed or refractory AML, optimal combination strategies are an important area of investigation. MLN4924 (pevonedistat) is a novel small molecule inhibitor of NEDD8-activating enzyme (NAE), which is involved in the ubiquitin-proteasome system and responsible for protein turnover within cells and has significant impact on cell growth and survival. Preclinical studies in AML have shown that exposure to MLN4924 (pevonedistat), especially when combined with AML chemotherapies including cytarabine or azacitidine, results in potent cell death. Further, a phase I study of MLN4924 (pevonedistat) combined with azacitidine in adults with AML demonstrated that the regimen was well tolerated, and that the combination of the two drugs resulted in higher complete remission rates compared to rates previously observed with either of the drugs alone. This is a phase I feasibility study of MLN4924 (pevonedistat) in combination with azacitidine followed by fludarabine and cytarabine for children with refractory or recurrent AML. MLN4924 (pevonedistat) will be administered in combination with azacitidine, fludarabine, and cytarabine in a 35-day cycle. A total of 2 cycles will be allowed. Once the recommended phase 2 dose (RP2D) is determined, a dose-expansion cohort will further assess the safety of this combination. This clinical trial is critical to evaluating this novel agent in AML and determining the safety of this combination strategy in relapsed AML in efforts to improve outcomes for this group of patients.

EXPERIMENTAL DESIGN SCHEMA

ALL PATIENTS:



*Only for patients who are CNS2 or CNS3. Patients will receive IT cytarabine or ITTs until the CNS is clear of blasts on 2 consecutive lumbar punctures

1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

1.1 Primary Aims

1.1.1 To evaluate the tolerability and feasibility of MLN4924 (pevonedistat) added to the 3-drug backbone of azacitidine (aza), fludarabine, and cytarabine re-induction for pediatric patients with recurrent/refractory AML and MDS.

1.1.2 To define and describe the toxicities of MLN4924 (pevonedistat) when given in combination with azacitidine, fludarabine, and cytarabine to pediatric patients with relapsed/refractory AML and MDS.

1.1.3 To characterize the pharmacokinetics of MLN4924 (pevonedistat) in children with recurrent or refractory AML and MDS.

1.2 Secondary Aim

1.2.1 To describe the antitumor activity of MLN4924 (pevonedistat) in combination with azacitidine, fludarabine, and cytarabine within the confines of a feasibility study.

1.3 Exploratory Aims

1.3.1 To describe the effect of MLN4924 (pevonedistat) administered on this schedule on mRNA transcript levels of genes known to be induced by MLN4924 (pevonedistat) mediated NAE inhibition.

1.3.2 To describe the effect of MLN4924 (pevonedistat) on NEDDylation of proteins in the NEDD8 pathway that are likely to be affected by NAE inhibition with MLN4924 (pevonedistat).

2.0 BACKGROUND

2.1 Introduction/Rationale for Development

MLN4924 (pevonedistat) is a novel small molecule inhibitor of NEDD8-activating enzyme (NAE) that is currently under development for patients with hematologic and solid malignancies. The NEDD8 conjugation pathway is involved in the ubiquitin-proteasome system (UPS), which is responsible for protein turnover within cells. The NAE is an essential component of the NEDD8 conjugation pathway, controlling the activity of a subset of UPS E3 ligases that regulate the timely ubiquitination of proteins with key roles in cell cycle progression and a number of cellular processes integral to cell growth, proliferation, and survival. In preclinical studies in both solid and hematologic cancer cell lines, MLN4924 (pevonedistat) resulted in NAE inhibition, decreased NEDD8-cullin levels, and an increase in ubiquitin ligases that require NEDD8 for activation.[1,2] In most cases, exposure to MLN4924 (pevonedistat) resulted in DNA damage and cell death through apoptosis.[3] AML samples with cycling cells were more sensitive to NAE inhibition than non-cycling cells. Phase 1 studies of MLN4924 (pevonedistat) in adults with hematologic and non-hematologic malignancies have suggested promising activity with minimal adverse effects when administered on specific

dosing schedules.[1,4] *In vitro* and *in vivo* evaluation by the Pediatric Preclinical Testing Program (PPTP) in cell lines and xenograft models demonstrated inhibition of tumor growth in some malignancies.[5] Clinical development with MLN4924 (pevonedistat) in adults is currently focused on patients with AML and MDS due to the encouraging activity and safety in combination with azacitidine, as well as additional therapies in this patient population in Phase 1 and Phase 2 clinical trials.[6,7]

The chemotherapy backbone of fludarabine (Flu) and cytarabine (AraC) has become a standard re-induction regimen among pediatric patients with relapsed AML. The International BFM group conducted a randomized trial that compared Flu/AraC + filgrastim vs. Flu/AraC + filgrastim + daunoXome that randomized 394 patients, providing the largest amount of statistically significant data evaluating cytarabine based regimens. Following 2 courses of therapy with Flu/AraC vs Flu/AraC+daunoXome, the CR was 59% vs 69% respectively (p=0.07), with no differences in overall survival at 36% vs. 40% respectively (p=0.54).[8] However, among patients with core binding factor AML there was improvement in survival observed among patients receiving daunoXome. Many patients are at risk for treatment-related cardiotoxicity due to the cumulative anthracycline exposure during initial therapy, as well as the total body irradiation for patients who have undergone hematopoietic stem cell transplant. Thus, the development of effective non-anthracycline regimens is critical for patients with relapsed AML. For these reasons, the Flu/AraC regimen has now become the standard salvage backbone for which novel agents are evaluated within COG as well as other cooperative groups. Single agent MLN4924 (pevonedistat) resulted in a 9% CR/CRi rate compared to 39% for azacitidine + MLN4924 (pevonedistat), and 44% among patients who were evaluable for disease.[6,7] Given the encouraging data from early phase clinical trials with the combination of azacitidine + MLN4924 (pevonedistat), there is compelling rationale to move this combination forward in AML.

Aberrant DNA methylation has been associated with disease progression and drug resistance, thus providing rationale for the potential of a DNA hypomethylating agent such as azacitidine to be added into chemotherapy regimens.[9,10] Hypomethylating agents such as azacitidine have been found to act through a variety of mechanisms with anti-leukemic potential, including but not limited to induction of global hypomethylation, downregulation of oncogenes, reactivation of tumor suppressors, and increasing sensitivity to cytotoxic agents.[11-13] There is also preclinical and clinical data to support the safety and potential increase in efficacy of azacitidine in combination with fludarabine and cytarabine in AML. *In vivo* studies have demonstrated that azacitidine administered prior to high dose AraC can result in hypomethylation and increased expression of certain genes, including deoxycytidine kinase (dCK), which results in increased cellular ara-CTP concentrations and sensitivity to AraC.[8,14] A phase 1 trial evaluating azacitidine in combination with fludarabine and cytarabine in pediatric AML found this regimen to be safe and well tolerated with no excess toxicity compared to what is seen with standard AML salvage regimens, particularly Flu/AraC alone.[15] Pharmacodynamic studies demonstrated a decrease in methylation following azacitidine exposure in the peripheral blood of all patients treated with this regimen.[15] Taken together, this pre-clinical data as well as phase 1 adult and pediatric studies demonstrate the biologic rational for azacitidine given with MLN4924 (pevonedistat), and demonstrate the safety of this regimen. The azacitidine prime prior to standard chemotherapy is also being evaluated in the upfront setting of the St. Jude's trial AML16 (NCT03164057). Given the importance of the epigenome in AML and the global hypermethylation that is often seen in AML, there is significant interest in

the use of epigenetic modulation in combination with chemotherapy. This trial will further the COG's investigation in the safety and potential efficacy of this strategy. Based on results of this study, the cassette of MLN4924 (pevonedistat) + azacitidine in combination with flu/AraC could move into the phase II setting where it is evaluated against the combination of azacitidine + Flu/AraC to determine the efficacy signal attributable to the MLN4924 (pevonedistat) + azacitidine combination.

Regimens used in relapsed AML are very intensive with known toxicities, especially myelosuppression. Given the intensity of myelosuppression for many relapsed AML regimens, there is no consensus measure of what duration is excessively toxic. Recent review of the COG trial AAML0531 is in line with TACL's findings, as on this study the median time to platelet > 50,000 and ANC > 500 was 38 and 37 days, respectively, and evaluation of approximately 2 standard deviations of this is approximately 50 days. More recent COG trials for relapsed AML, including the current first line relapse trial, have set a duration of greater than 50 days from the start of therapeutic cycle as excessively myelosuppresive and a DLT based on the recovery times for multi-agent intensive regimens. Fludarabine and cytarabine is comparable in intensity to this regimen, therefore for this trial a time of 50 days from the start of therapy without hematologic recovery (ANC>500 and a non-transfusion platelet count > 20,000) as a hematologic DLT.

2.2 Preclinical Studies

2.2.1 Antitumor Activity

There is strong biologic rationale to utilize MLN4924 (pevonedistat) in AML. *In-vitro* studies of MLN4924 (pevonedistat) as a single agent demonstrate its ability to induce death of AML cells through multiple pathways, including NF-κB inhibition, reactive oxygen species generation, and DNA damage.[16,17] There exists biologic rationale to combine MLN4924 (pevonedistat) with cytarabine, as MLN4924 (pevonedistat) disrupts nucleotide metabolism and promotes increased incorporation of cytarabine into the DNA of AML cells, and the combination led to observed synergy *in vitro* and increased survival for AML xenograft models.[16,18] Among 4 AML cell lines tested, all showed increased cell death when treated with the drug combination, as well as patient samples (n=10) with combination indexes (CI) ranging from 0.5-0.8 across all combinations tested, all demonstrating synergy (CI < 1).[18] Importantly, there was no difference seen between primary patient samples with prior exposure to chemotherapy (n=6) compared to treatment naive samples (n=4). Preclinical data from *in vitro* studies demonstrates synergistic activity of MLN4924 (pevonedistat) administered in combination with cytarabine.[16,18] The combination of azacitidine and MLN4924 (pevonedistat) was evaluated in an AML xenograft model and the combination demonstrated synergy when compared to monotherapy with a significant decrease in tumor burden ($p<0.05$).[19]

MLN4924 (pevonedistat) administration in tumor-bearing immunocompromised mice has demonstrated anti-tumor activity in AML xenografts, as demonstrated by stable disease regression and inhibition of NEDDylated cullins.[17] Treatment with MLN4924 (pevonedistat) resulted in dose dependent inhibition of the neddylation of cullins, as well as the stabilization of cullin-dependent ligase substrates Nrf-2 and Cdt1, and a DNA damage response.[2]

Pharmacodynamic studies have demonstrated that MLN4924 (pevonedistat) exposure results in increased levels of the protein ribonucleotide reductase (RRM2), which can be antagonized by azacitidine, which may result in increased sensitivity to MLN4924 (pevonedistat). In vitro studies in AML cell lines demonstrated the ability of azacitidine to counter the normally seen increase in RRM2 following MLN4924 (pevonedistat).[19] The combination was evaluated in 7 AML cell lines and resulted in synergy (CI < 1) when evaluating cell viability.[19]

2.2.2 Animal Toxicology

The non-clinical safety profile of MLN4924 (pevonedistat) has been characterized when given by SubQ injection or 30 minute IV infusion in Sprague Dawley rats and by 30 minute IV infusion in beagle dogs. The lethal dose in rats in a SubQ repeat dose 5 day study was 200 mg/kg (1200 mg/m^2) within 24 hours after a single dose. Additionally moribundity requiring euthanasia within 24 hours after a dose was observed in dogs dosed at 40 mg/kg (800 mg/m^2).[20]

The highest non-severely toxic dose (HNSTD) of MLN4924 (pevonedistat) when administered cyclically (2 cycles of 5 days of dosing followed by a 14 day rest period or 5 cycles of 4 doses given every other day followed by a 14 day rest period) was 15 mg/kg (300 mg/m^2) in dogs and 60 mg/kg (360 mg/m^2) in rats. The primary dose limiting toxicity of MLN4924 (pevonedistat) in rats and beagle dogs was GI toxicity leading to electrolyte imbalances and dehydration and complications associated with bone marrow suppression. An acute phase-like response was also observed presenting with alterations in body temperature, increased fibrinogen, decreased albumin, alterations in circulating neutrophils, and increased neutrophil infiltration in multiple tissues (dogs only). Decreased blood pressure, increased heart rate, and shortened PR and QT intervals followed by an increased diastolic blood pressure were also noted. Myocardial, renal, and hepatotoxicity seen at doses above the maximum tolerated dose (MTD) in rats were correlated with sepsis. Other adverse effects observed were injection site necrosis of skin and soft tissues with SubQ administration, changes in trabecular bone formation and changes in serum chemistry. Most MLN4924 (pevonedistat) related adverse effects resolved during the 14 day rest period or were resolving at the completion of the 14 days and are considered reversible.[20]

Microscopic changes noted in male and female reproductive organs in rats and dogs indicate MLN4924 (pevonedistat) represents a significant reproductive and developmental hazard. MLN4924 (pevonedistat) was not mutagenic in a bacterial reverse mutation (Ames) test.[20] Please refer to the Investigator's brochure for full details of preclinical toxicology studies.

2.2.3 Preclinical Pharmacokinetic Studies

In vitro, MLN4924 (pevonedistat) is predominantly metabolized by CYP3A4, with small contribution from the CYP2D6. Drug-drug interaction studies indicated CYP3A4 inhibitors had no clinically meaningful effects on MLN4924 (pevonedistat) pharmacokinetics, however, there is potential for drug-drug interactions if MLN4924 (pevonedistat) is coadministered with drugs that are CYP3A4 inducers. MLN4924 (pevonedistat) is a weak and reversible inhibitor of CYP2B6 and 2C8. The major elimination pathway of MLN4924 (pevonedistat)

in animals was through the hepatic route. Animal studies have demonstrated that MLN4924 (pevonedistat) has been shown to be primarily excreted in the feces and excretion is almost complete by 24 hours postdose. MLN4924 (pevonedistat) has been shown to be a substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance protein 2 (MRP2).[20]

2.3 Adult Studies

2.3.1 Phase 1 Studies

To date, MLN4924 (pevonedistat) has been evaluated in multiple phase 1 studies as a single agent and with combination therapy in adults with both hematologic and non-hematologic malignancies. Results have demonstrated that MLN4924 (pevonedistat) is tolerated on an intermittent dosing schedule and has promising results for potential efficacy.

Two single agent studies in hematologic malignancies, including one for patients with AML or myelodysplastic syndrome (MDS), have evaluated MLN4924 (pevonedistat) across a range of dosing schedules as well as doses, ranging from 25 mg/m^2 – 147 mg/m^2. When MLN4924 (pevonedistat) was administered on days 1, 3, and 5 every 21 days in 27 patients, the maximum tolerated dose (MTD) was determined to be 59 mg/m^2.[7] The most common adverse events (AE) on this schedule were diarrhea (52%), pyrexia (44%), febrile neutropenia (41%), decreased appetite (41%), fatigue (33%), myalgia (30%), increased AST (30%), and increased ALT (33%).[7] A variety of dose limiting toxicities (DLTs) occurred, including hepatic toxicity, hypotension, cardiac failure, GI necrosis, lactic acidosis, myocardial ischemia, acute renal failure, and morbiliform rash. For the 23 patients treated at or below the MTD for the schedule above, there were 2 complete remissions (CR, 9%) and additional 2 partial remissions (PR 8%), for a combined CR/PR rate of 17%.[7] An additional 26 patients were treated on alternate dosing regimen that administered MLN4924 (pevonedistat) on days 1, 4, 8, and 11 and the MTD was determined to be 83 mg/m^2 and there were 2 PRs observed (10%).

An additional trial evaluating MLN4924 (pevonedistat) in combination with azacitidine in older adult patients (≥ 60 years of age) with de novo AML has demonstrated an acceptable toxicity profile. This study administered azacitidine IV or subcutaneously for a total of 7 days on days 1-5, 8-9 (5 on/2 weekend off/2 on) at a dose of 75 mg/m^2 with MLN4924 (pevonedistat) administered on days 1, 3, and 5 in 28-day treatment cycles. MLN4924 (pevonedistat) doses of 20 mg/m^2 (n=55) and 30 mg/m^2 (n=6) dosing were evaluated and the MTD was determined to be 20 mg/m^2. A total of 61 patients have been treated on this study, receiving a median of 4 cycles of therapy (range of 1-33). The most common AEs were constipation (48%), nausea (42%) fatigue (42%), and anemia (39%). A majority of patients (n=53, 83%) experienced a ≥ grade 3 AE, with most common being anemia and febrile neutropenia (30% each), thrombocytopenia (23%), neutropenia (20%), and pneumonia (17%). There were DLTs observed in four patients (n=2 at 20 mg/m^2 and n=2 at 30 mg/m^2). One patient had elevated bilirubin, and the other 3 patients had elevated AST and ALT (maximum grade 3-4). For the 2 patients with transaminase elevation treated at the 20 mg/m^2 dose, this was a transient effect

that resolved spontaneously and the patients were successfully re-challenged at a lower dose and remained on study. The most common SAEs detected were febrile neutropenia (25%) and pneumonia (14%). These infectious events and myelosuppression are commonly observed in AML regimens. None of the on-study deaths (n=11) were attributed to MLN4924 (pevonedistat). A total of 64 patients were treated and included in the intent to treat (ITT) cohort, with a total of 52 patients evaluable for response. Among the ITT cohort, the CR/CRi rate was 39% (20 CR, 5 CRi) with 7 PRs for an overall response rate (ORR) of 50%. Among the patients evaluable for response, a CR/CRi rate of 48% was observed.[6]

2.3.2 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Pharmacokinetic studies with single agent MLN4924 (pevonedistat) have demonstrated that C_{max} and AUC_{24} do increase in a dose proportional manner when evaluated from 25-147 mg/m^2. However plasma concentrations are similar across a range of doses (25 -78 mg/m^2) after 12 hours of exposure and were detectable at 24 hours post-dose.[21] Pharmacodynamic (PD) studies with single agent MLN4924 (pevonedistat) have demonstrated induction of multiple target genes induced by MLN4924 (pevonedistat) mediated NAE inhibition across all dose levels tested.[1,7] Pharmacodynamic data across the various single-agent phase 1 MLN4924 (pevonedistat) trials provide evidence of pathway inhibition downstream of NAE and biological activity is seen across all doses tested (range 25-261 mg/m^2) in pharmacodynamics assays. Additional data of PK and PD studies of single agent MLN4924 (pevonedistat), including in the presence of moderate CYP3A4 inhibitor also demonstrated activity of MLN4924 (pevonedistat) at 8, 15, and 20 mg/m^2 doses. Pharmacodynamic evaluation of 8 genes of interest that are induced by NAE inhibition demonstrated an increase in gene expression relative to baseline in all genes. Importantly, positive increases in gene expression were most notable at the higher doses of 15 and 20 mg/m^2 as compared to the 8 mg/m^2 dose, where more variability was observed. Further, the time interval of maximal effect was seen at 4-8 hours following MLN4924 (pevonedistat) administration with a similar pattern between the 15 and 20 mg/m^2 doses.[22]

Preliminary PK studies of MLN4924 (pevonedistat) demonstrate no alterations in PK profiles in the presence of azacitidine compared to single agent MLN4924 (pevonedistat) as well as in the presence of other conventional chemotherapy agents.[6,23]

2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There is a currently accruing phase 1 study within COG (ADVL1615) evaluating MLN4924 (pevonedistat) in patients with relapsed/refractory solid tumors. The study is evaluating MLN4924 (pevonedistat) as a single agent and in combination with irinotecan and temozolomide. The study is currently accruing at dose level 2 (20 mg/m^2) and thus far no DLTs have been reported.

2.5 Overview of Proposed Pediatric Study

This is a feasibility study of MLN4924 (pevonedistat) in combination with azacitidine, fludarabine, and cytarabine for patients with recurrent or refractory AML or MDS. MLN4924 (pevonedistat) will be administered IV over 1 hour on days 1, 3, and 5 of a 35-day cycle at a starting dose of 20 mg/m^2 for patients $\geq$ 1 year of age. For patients < 1 year of age, MLN4924 (pevonedistat) will be administered IV over 1 hour on days 1, 3, and 5 of a 35-day cycle at a starting dose of 15 mg/m^2. For all patients, MLN4924 (pevonedistat) will be administered in combination with azacitidine (75 mg/m^2/dose for patients $\geq$ 1 year of age and 2.5 mg/kg/dose for patients < 1 year of age) daily x 5 days administered on days 1-5. Following completion of azacitidine and MLN4924 (pevonedistat), IV fludarabine (30 mg/m^2/dose for patients $\geq$ 1 year of age and 1 mg/kg/dose for patients < 1 year of age) infused over 30 minutes, and IV cytarabine (2000 mg/m^2/dose for patients $\geq$ 1 year of age and 67 mg/kg/dose for patients < 1 year of age) infused over 1-3 hours will be administered daily x 5 days, with cytarabine infusion to begin 4 hours after the start of fludarabine. A total of 2 cycles will be allowed. Once the RP2D is determined, a dose-expansion cohort will further assess the safety of this combination. Pharmacokinetics will be obtained in all patients while correlative studies will be obtained in consenting patients. Based on the results of this study, the efficacy of this combination will be further evaluated in a phase 2 trial for relapsed AML.

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. Bone marrow biopsy and/or aspirate must be obtained within 14 days prior to start of protocol therapy.

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: Patients must be ≥ 1 months and ≤ 21 years of age at the time of study enrollment.

4.1.2 Diagnosis:

4.1.2.1 Patients must have had histologic verification of AML at the original diagnosis. Patients must have one of the following:

a) Recurrent disease in ≥ 1st relapse with ≥ 5% blasts in the bone marrow (M2/M3) marrow OR immunophenotypic evidence of disease with ≥ 0.1% blasts detected by flow cytometry, OR evidence of recurrent cytogenetic or molecular abnormalities consistent with relapse, with or without extramedullary disease.

b) Refractory AML is defined as ≥ 5% blasts in the bone marrow (M2/M3) after ≥ 2 induction attempts (i.e., 2 cycles of chemotherapy).

4.1.2.2 Patients with advanced MDS, including MDS that has progressed to AML, and have experienced relapse or are refractory after ≥ 1 course of induction therapy, are eligible.

4.1.3 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 50 for patients ≤ 16 years of age (See Appendix I).

4.1.4 Prior Therapy:

4.1.4.1 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. 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.

- ≥ 14 days must have elapsed after the completion of other cytotoxic therapy, with the exception of hydroxyurea, for patients not receiving standard maintenance therapy. Additionally, patients must have recovered from all acute toxic effects of prior therapy.

  NOTE: Cytoreduction with hydroxyurea must be discontinued ≥ 24 hours prior to the start of protocol therapy.

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. 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.

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

f. 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.

g. Cellular Therapy: ≥ 30 days after the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.)

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

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

j. Patients must not have received prior exposure to MLN4924 (pevonedistat).

4.1.5 Organ Function Requirements

4.1.5.1 Adequate Renal Function Defined as:
- Creatinine clearance or radioisotope GFR ≥ 60ml/min/1.73 m^2 or
- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female

1 month to < 6 months	0.4	0.4
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.

4.1.5.2 Adequate Liver Function Defined as:
- Bilirubin (sum of conjugated + unconjugated) ≤ upper limit of normal (ULN) for age.
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 X ULN. For the purpose of this study, the ULN for SGPT is 45 U/L.

4.1.5.3 Adequate Cardiac Function Defined As:
- Shortening fraction of ≥ 27% by echocardiogram, or
- Ejection fraction of ≥ 50% by echocardiogram or radionuclide angiogram
- No ventricular or supraventricular arrhythmia on EKG
- Prolonged rate corrected QT (QTc) interval < 500 msec

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

4.1.5.5 Adequate Coagulation Defined As:
- INR ≤ 1.5

4.1.5.6 Adequate Bone Marrow Function Defined As:
- Hemoglobin > 8.0 g/dL (may receive RBC transfusions)

4.1.6 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

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as seen in animal/human studies, *OR* because there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Males or females of reproductive potential may not participate unless they have agreed to use 1 highly effective and 1 additional effective (barrier) method of contraception at the same time for the duration of study therapy and for 4 months after the completion of MLN4924 (pevonedistat) administration. True abstinence,

when this is in line with the preferred and usual lifestyle of the subject, is acceptable. 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 Concomitant Medications

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

4.2.2.2 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible [except hydroxyurea, which may be continued until 24 hours prior to start of protocol therapy].

4.2.2.3 Anti-GVHD agents post-transplant:
Patients who are receiving cyclosporine, tacrolimus or other systemic agents to prevent graft-versus-host disease post bone marrow transplant are not eligible for this trial. Topical immunosuppressive agents (e.g. topical steroids) are allowed. Physiologic replacement of hydrocortisone is allowed.

4.2.2.4 Patients who are taking drugs that are strong CYP3A4 inducers and cannot be switched to alternative drugs 14 days prior to enrollment are not eligible. Strong inducers of CYP34 are not permitted during the study. See Appendix IX for more details.

4.2.3 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.

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

4.2.5 Patients with uncontrolled high blood pressure (i.e., ≥ 99% for age, see Appendix XI) are not eligible.

4.2.6 Patients with any of the following diagnoses:
- Acute promyelocytic leukemia
- Down syndrome
- Juvenile myelomonocytic leukemia

4.2.7 Infection: Patients who have a documented active uncontrolled infection are not eligible.

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

4.2.9 Patients with HIV are not eligible unless they meet all of the following criteria:
- CD4 count > 350 cell/mm^3
- Undetectable viral load
- Maintained on modern therapeutic regimens utilizing non-CYP-interactive agents
- No history of AIDS-defining opportunistic infections

4.2.10 Female patients who intend to donate eggs (ova) during the course of this study or 4 months after receiving their last dose of study drug(s) are not eligible.

4.2.11 Male patients who intend to donate sperm during the course of this study or 4 months after receiving their last dose of study drug(s) are not eligible.

5.0 TREATMENT PROGRAM

5.1 Overview of Treatment Plan

The primary purpose of this feasibility study is to evaluate the safety and toxicity profile of MLN4924 (pevonedistat) in combination with azacitidine, fludarabine, and cytarabine in children with relapsed or refractory AML or MDS and to recommend a phase 2 dose for use in further studies. A rolling 6 design will be utilized. Patients will receive 1 dose of intrathecal cytarabine with a diagnostic lumbar puncture to be performed prior to the start of each cycle of therapy.

For patients $\geq$ 1 year of age, MLN4924 (pevonedistat) will be administered at 20 mg/m^2/dose intravenously (IV) on days 1, 3 and 5. Azacitidine will be administered at 75 mg/m^2/dose IV once daily on days 1-5. On days 1, 3, and 5 when both drugs are administered, azacitidine will be administered first followed by MLN4924 (pevonedistat) infusion. The infusion of MLN4924 (pevonedistat) will begin between 30-60 minutes after completion of IV azacitidine. Following completion of azacitidine and MLN4924 (pevonedistat), fludarabine 30 mg/m^2/dose IV once daily and cytarabine 2000 mg/m^2/dose IV once daily will be administered on days 6-10. Cytarabine infusion will begin 4 hours after the start of fludarabine.

For patients < 1 year of age, MLN4924 (pevonedistat) will be administered at 15 mg/m^2/dose intravenously (IV) on days 1, 3, and 5. Azacitidine will be administered at 2.5 mg/kg/dose IV once daily on days 1-5. On days 1, 3, and 5 when both drugs are administered, azacitidine will be administered first followed by MLN4924 (pevonedistat) infusion. The infusion of MLN4924 (pevonedistat) will begin between 30-60 minutes after completion of IV azacitidine. Following completion of azacitidine and MLN4924 (pevonedistat), fludarabine 1 mg/kg/dose IV once daily and cytarabine 67 mg/kg/dose IV once daily will be administered on days 6-10. Cytarabine infusion will begin 4 hours after the start of fludarabine.

Patients without additional evidence of CNS disease (CNS1) do not require additional CNS-directed therapy during the cycles. Patients with blasts detected in the CNS (CNS2/3) will receive additional intrathecal chemotherapy with IT cytarabine or IT triple therapy (cytarabine, hydrocortisone, methotrexate) per institutional standards at a schedule of 2x/weekly until the CNS is clear of blasts on 2 consecutive LPs, with a minimum of 4 IT cytarabine or IT triple (ITT) doses administered.

NOTE: Central venous access in the form of a double lumen Broviac or Hickman is highly recommended.

	Day 0	1	2	3	4	5	6	7	8	9	10	11-34	35
IT Cytarabine (all patients)	X												
Azacitidine		X	X	X	X	X							Disease Evaluation
MLN4924 (Pevonedistat)		X		X		X							
Fludarabine							X	X	X	X	X		
Cytarabine							X	X	X	X	X		
IT Cytarabine **OR** ITT* (CNS2/3)									X*			X*	

*For patients with CNS 2/3 status, IT cytarabine or ITT should be administered 2x/weekly until the CNS is clear of blasts on 2 consecutive LPs, with a minimum of 4 IT cytarabine/IT triple doses administered. This should begin on Day 8 and should be repeated 2x/weekly with not less than 3 days between doses, thus any necessary subsequent doses should be given starting on Day 11. Days of therapy may vary depending on scheduling.

A cycle of therapy is considered to be 35 days. A cycle may be repeated for a total of 2 cycles, up to a total duration of therapy of approximately 4 months.

Drug doses of MLN4924 (pevonedistat), azacitidine, fludarabine, and cytarabine should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle. Drug doses of intrathecal cytarabine and intrathecal triples should be based on the age at the time of administration.

See Appendix VIII for Therapy Delivery Maps for each cycle.

5.2 Treatment Details (Cycles 1 & 2)

Intrathecal cytarabine: IT
All patients will receive 1 dose of IT cytarabine using age-based dosing below at the time of diagnostic lumbar puncture, or on Day 0 of each cycle. Patients may be given intrathecal cytarabine up to 1 week prior to Day 1, but at least 24 hours prior to the start of MLN4924 (pevonedistat) and azacitidine on Day 1. If IT cytarabine is given prior to enrollment, a separate institutional consent must be obtained.

Age-based dosing:

Age (yrs)	**Dose**
< 1	20 mg
1-1.99	30 mg
2-2.99	50 mg
≥ 3	70 mg

Triples (Methotrexate/Hydrocortisone/Cytarabine): IT
For CNS2/3 patients only. IT triples may be given instead of IT cytarabine for CNS2/3 patients in Cycle 1 after the Day 0 IT cytarabine dose per the details described below.

Age-based dosing:

Age (yrs)	**Dose**
<1	MTX: 7.5 mg, HC: 7.5 mg, ARAC: 15 mg
1-1.99	MTX: 8 mg, HC: 8 mg, ARAC: 16 mg
2-2.99	MTX: 10 mg, HC: 10 mg, ARAC: 20 mg
3-8.99	MTX: 12 mg, HC: 12 mg, ARAC: 24 mg
≥ 9	MTX: 15 mg, HC: 15 mg, ARAC: 30 mg

For CNS2 or CNS3 patients:
Patients with CNS2 or CNS3 involvement at screening will receive additional intrathecal chemotherapy with IT cytarabine or IT triples (doses as above) at a twice weekly schedule until the CNS is clear of blasts on 2 consecutive LPs. The administration of IT cytarabine vs IT triples is up to the treating physician's discretion. A minimum of 4 and a maximum of 6 intrathecal treatments may be given. This count includes the pre-study/Day 0 dose. Subjects who have persistent CNS disease despite 6 doses of IT cytarabine or IT triples will be off study treatment and considered treatment failures (See Section 12.2.5). See Section 12.3 for definitions of CSF involvement.

Azacitidine: IV over 15 minutes once daily
Days: 1-5
Dose: Age based dosing

Age	Dose
<1 year	2.5 mg/kg/dose
≥ 1 year	75 mg/m^2/dose

Note: infusion must be completed within 1 hour of vial reconstitution
On Days 1, 3, and 5 azacitidine will be given 30-60 minutes before MLN4924 (pevonedistat) infusion. See details of the timing below.

MLN4924 (Pevonedistat)*: IV over 60 minutes
Days: 1, 3, and 5
Starting dose: 20 mg/m^2 for patients ≥ 1 year of age; 15 mg/m^2 for patients < 1 year of age (Dose Level 1). See Dosing Schema in Section 5.4.

***NOTE:** Give MLN4924 (pevonedistat) 30 – 60 minutes after the completion of the azacitidine infusion. If MLN4924 (pevonedistat) dosing is delayed, a minimum of 1 full calendar day between any 2 doses should be maintained.

Fludarabine: IV over 30 minutes once daily
Days: 6-10
Dose: Age based dosing

Age	Dose
< 1 year	1 mg/kg/dose
≥ 1 year	30 mg/m^2/dose

High Dose Cytarabine: IV infusion over 1-3 hours once daily
Days: 6-10
Dose: Age based dosing (begin 4 hours after start of fludarabine)

Age	Dose
< 1 year	67 mg/kg/dose
≥ 1 year	2000 mg/m^2/dose

Please note: Following/during high-dose cytarabine, chemical conjunctivitis may occur. Administer steroid eye drops (0.1% dexamethasone or 1% prednisolone ophthalmic solution), 2 drops to each eye every 6 hours, beginning immediately before the first dose and continuing for 24 hours after the last dose. If patient does not tolerate steroid eye drops, artificial tears may be administered on an every 2-4 hour schedule.

See the Chemotherapy Administration Guidelines (CAG) on the COG website at: https://cogmembers.org/_files/disc/Pharmacy/ChemoAdminGuidelines.pdf for special precautions and suggestions for patient monitoring during the infusion. As applicable, also see the CAG for suggestions on hydration, or hydrate according to institutional guidelines.

5.3 Criteria for Starting Cycle 2

Patients may proceed to cycle 2 following completion of cycle 1 disease assessment if stable or greater response and if non-hematologic toxicities probably or definitely related to MLN4924 (pevonedistat) recover to ≤ grade 2. Bilirubin, ALT, and AST must be ≤ Grade 1 or at the patient's baseline values prior to starting Cycle 2.

NOTE: See Appendix III for Toxicity Specific Grading.

- Patients will have disease assessment on Day 36-39 of Cycle 1. If a bone marrow aspirate cannot be evaluated (dry tap, no spicules), a follow-up bone marrow aspirate and biopsy must be performed within 2 weeks to assess cellularity and response.
- If aspirate and/or biopsy results indicate hypocellular marrow (<10% cellularity on biopsy), then continue to repeat bone marrow aspirate and/or biopsy not less than once every 14 days until response can be assessed.
- If count recovery is noted within 14 days of an unevaluable marrow, there is no need to repeat the marrow to confirm response.
- If the patient meets criteria for CR, CRp, or CRi after Cycle 1 then the patient can proceed to Cycle 2 (See Section 12.2 for definitions of response)
- If the bone marrow aspirate and/or biopsy performed after Cycle 1 reveals ≥ 5% but ≤ 25% blasts, then the patient should proceed to Cycle 2 of chemotherapy

5.4 Dosing Schema

5.4.1 Dose Confirmation Schema

The starting dose will be 20 mg/m^2 for patients ≥ 1 year of age (Dose Level 1) with dose levels for subsequent groups of patients as follows:

Dose Level	MLN4924 (Pevonedistat) Dose (mg/m^2)
-1	15 mg/m^2
1*	**20 mg/m^2**

* Starting Dose Level

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

Dose Level	MLN4924 (Pevonedistat) Dose (mg/m^2)
-1	10 mg/m^2
1*	**15 mg/m^2**

* Starting Dose Level

There will be no escalations beyond Dose Level 1 (20 mg/m^2), as adult studies examining doses higher than 20 mg/m^2 observed excess toxicity without any apparent disease benefit and no significant differences in pharmacokinetic parameters to suggest significant increase in efficacy.[24]

If the maximally tolerated dose (MTD) has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at 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 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 website (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 that are possibly, probably or definitely attributable to protocol therapy. The DLT observation period for the purposes of dose-confirmation will be the first cycle of therapy.

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

5.6.1 Non-hematological dose-limiting toxicity:

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 or 4 elevation of ALT/AST that returns to Grade ≤ 1 within 14 days. NOTE: For the purposes of this study the ULN for ALT is defined as 45 U/L regardless of baseline and for AST is defined as 50 U/L regardless of baseline. See Appendix III for values that represent thresholds between CTCAE grades.

- Grade 3 or 4 electrolyte abnormalities that resolve, with or without supplementation intervention, to ≤ Grade 2 within 72 hours. Electrolyte supplementation is encouraged.
- Grade 3 arthralgia/myalgia that returns to Grade ≤ 2 within 5 days on analgesics
- Grade 3 or 4 fever, febrile neutropenia, or infection with or without hospitalization
- Grade 3 tumor lysis syndrome
- Alopecia
- Grade 3 maculo-papular or morbiliform rash that resolves to ≤ Grade 2 within 7 days
- Grade 3 mucositis that resolves (with or without supportive care) to ≤ Grade 2 within 14 days
- Grade 3 fatigue or anorexia responsive to supportive care within 7 days
- Grade 3 nausea, vomiting, and/or diarrhea responsive to supportive care within 72 hours
- Early intervention with TPN or enteral tube feeding for anorexia, nausea, or concern for poor nutritional status

5.6.2 Hematological dose-limiting toxicity:

Hematological dose limiting toxicity attributable to protocol therapy is defined as failure to recover to a peripheral ANC > 500/m^3 and platelets > 20,000/mm^2 by 50 days from the start of fludarabine and cytarabine administration, not due to presence of leukemia or severe infection (defined as Grade ≥ 3).

- **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. Patients may receive up to 2 cycles of chemotherapy.

6.1 Dose Modifications for Hematological Toxicity

6.1.1 Patients who experience a hematologic dose limiting toxicity (see Section 5.6.2), defined as failure to recover peripheral ANC > 500/uL and non-transfusion dependent platelet count > 20,000/uL due to documented bone marrow aplasia/hypoplasia (not due to malignant infiltration or Grade 3 infection) for greater than or equal to 50 days from the start of fludarabine and cytarabine administration, will be allowed to proceed at the discretion of the treating physician and study chair with cycle 2 at MLN4924 (pevonedistat) dose level -1. The patient's dose for azacitidine, fludarabine, and cytarabine will remain unchanged.

6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 Patients will have ALT/AST/bilirubin evaluated prior to each planned dose of MLN4924 (pevonedistat) in order to determine whether the scheduled dose

should be administered. It is anticipated that ALT and AST may be elevated for approximately 48 hours following the end of the 1st MLN4924 (pevonedistat) infusion.
NOTE: See Appendix III for toxicity grading table.

If a patient experiences > Grade 3 elevation of ALT/AST on or after Cycle 1, Day 1 then the Cycle 1, Day 3 MLN4924 (pevonedistat) dose should not be given. If ALT/AST returns to ≤ Grade 1 or baseline values by Day 5 then the patient should receive their Day 5 MLN4924 (pevonedistat) dose and this will not be considered a DLT. If ALT/AST does not return to ≤ Grade 1 or baseline values by Day 5 then MLN4924 (pevonedistat) should be held and this will be considered a DLT. Persistent elevations of ALT/AST > Grade 2 beyond 2 days between any other doses after Cycle 1, Day 1 will be considered a DLT.

6.2.2 Patients who experience a dose limiting toxicity during cycle 1 that resolves to baseline or < Grade 1 at the time of next cycle can proceed with the next cycle at dose level -1.

6.3 Modifications and Supportive Care Recommendations for Toxicity Related to Protocol Therapy (Cycle 1 and Cycle 2)

6.3.1 Neurological Toxicity

The most common neurotoxicity related to fludarabine or cytarabine administration is an acute cerebellar syndrome that may manifest itself as ataxia, nystagmus, or dysarthria. However, seizures and encephalopathy have also occurred following therapy with high dose cytarabine. Patients experiencing Grade 3 or 4 cerebellar toxicity should be removed from protocol therapy.

6.3.2 Ara-C Syndrome including Fever, Rash, or Conjunctivitis

Do not withhold cytarabine for fever if it is likely to have been caused by the cytarabine. However, blood cultures should be obtained even if fever is thought to be likely due to cytarabine. Institution of antibiotics for fever associated with cytarabine infusion is at the discretion of the treating physician (see fever management recommendations in the COG Supportive Care Guidelines).

For rash or conjunctivitis, withhold cytarabine for Grade 3-4 toxicity until resolved to ≤ Grade 1. Make up missed doses and consider concurrent treatment with hydrocortisone or dexamethasone, and/or with dexamethasone ophthalmic drops for conjunctivitis only.

6.3.3 Renal Toxicity

6.3.3.1 Cytarabine

Patients with nephrotoxicity secondary to antibiotics, or antifungals, may have prolonged excretion of cytarabine leading to more severe marrow and extramedullary toxicity.

- Patients with a serum creatinine > 2 mg/dL or > 2x normal for age should be hydrated orally or intravenously. Following hydration, the patient must have a creatinine clearance ≥ 60 mL/min/1.73m² as measured preferably by a nuclear GFR scan, timed urine collection for

creatinine clearance, or calculated by the Schwartz formula before proceeding with cytarabine therapy.

- If the creatinine clearance is abnormal (< 60 mL/min/1.73m^2) then Cycle 2 high dose cytarabine should be reduced by 50% for each daily dose. With this approach, previous research has shown the prevention of subsequent neurotoxicity in recipients of high dose cytarabine in the face of renal insufficiency.[25]

6.3.3.2 **Fludarabine**

Renal clearance accounts for about 40% of the total body clearance of fludarabine and clearance of the primary active metabolite is decreased in patients with renal impairment. Renal elimination appears to become more important at high dosages of the drug. The dose of fludarabine needs to be adjusted in patients with moderate renal impairment. The following are suggested guidelines for dose adjustment of fludarabine in renal impairment:

GFR > 50 mL/minute/1.73m^2: no adjustment required
GFR 30-50 mL/minute/1.73m^2: administer 80% of the dose
GFR < 30 mL/minute/1.73m^2: not recommended
Hemodialysis: administer 25% of the dose

Continuous ambulatory peritoneal dialysis (CAPD): not recommended
Continuous renal replacement therapy (CRRT): Administer 80% of dose[26]

6.3.4 Hand-Foot Syndrome

Hand-foot syndrome has been reported in patients treated with high-dose cytarabine. Patients who develop hand-foot syndrome may receive topical emollients (such as Aquaphor) as well as topical or systemic steroids or antihistamines if appropriate. Oral administration of vitamin B6 (pyridoxine) can also be used for these patients- BSA < 0.5 m^2: 50 mg per day; BSA 0.5-1.0 m^2: 100 mg per day; BSA 1.1-1.5 m^2: 200 mg per day, and BSA > 1.5 m^2: 300 mg per day.

6.3.5 MLN4924 (pevonedistat) dose modification for hepatic toxicity:

AST, ALT, and bilirubin should be checked and read prior to each dose of MLN4924 (pevonedistat) and then weekly.

If a patient experiences ≥ Grade 3 elevation of ALT/AST/bilirubin that does not return to ≤ Grade 1 or baseline prior to the next dose of MLN4924 (pevonedistat), the dose will be held and this will be considered a DLT. However, patients can still receive azacitidine as scheduled and can receive subsequent fludarabine and cytarabine if ALT ≥ Grade 3 after discussion with study chair. NOTE: See Appendix III for values that represent thresholds between CTCAE grades.

Patients who experience a dose limiting toxicity during cycle 1 that resolves to baseline or ≤ Grade 1 at the time of next cycle can proceed with the next cycle at dose level -1.

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 7.5 for drugs that should not be used concomitantly due to potential interactions with MLN4924 (pevonedistat). For COG Supportive Care Guidelines see: https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines under Standard Sections for Protocols.

The use of GCSF is not required on this protocol, however filgrastim or biosimilar can be initiated per discretion of the treating physician in the setting of serious confirmed (culture proven) or suspicious infection. The use of filgrastim (G-CSF) or biosimilar is allowed at the treating physician's discretion to enhance neutrophil recovery when clinically indicated. If the treating physician determines that filgrastim use is indicated in Cycle 1, the pegylated formulation (pegfilgrastim) should not be used.

Pneumocystis Jirovecii pneumonia (PJP) prophylaxis: Patients should receive PJP prophylaxis with trimethoprim/sulfamethoxazole 5 mg/kg/day divided BID (max: 160 mg PO BID) for 2-3 consecutive days a week, or per institutional practice, until the end of protocol therapy.

Antifungal prophylaxis

Antifungal agents per institutional guidelines should be administered when ANC falls below 200/µL and continued until count recovery. See Section 7.4.2 on CYP3A4 inducers and inhibitors for guidelines regarding concurrent administration with MLN4924 (pevonedistat).

Hospitalization/Hospital Environment

Hospitalization following each cycle of chemotherapy is strongly recommended until the absolute phagocyte count (sum of the neutrophils, bands and monocytes) rises for 2 successive days, and the patient is afebrile and clinically stable. An additional discharge criterion of an absolute neutrophil count (ANC) of at least 200/µL is also suggested.

It is recommended that patients should be assigned to rooms with special air filtration systems such as high efficiency particulate air filters (HEPA) or clean-air rooms with constant positive pressure airflow if at all possible.

Tumor Lysis Syndrome

Prophylaxis for tumor lysis syndrome (TLS) should be considered for patients at risk of developing rapid tumor lysis (e.g., patients with a high tumor burden or a higher number of circulating malignant cells). These patients should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for

patients who develop signs and symptoms consistent with rapid tumor lysis.

7.4 Concomitant Medications

7.4.1 Corticosteroid Therapy

Corticosteroids should not be used as anti-emetic therapy. Corticosteroid therapy is not permissible except for the following indications:

- As treatment or prophylaxis for anaphylactic reactions
- As a treatment for symptoms of ARA-C syndrome including fever, rash, or conjunctivitis (see Section 6.3.2)
- Suspected or confirmed adrenal insufficiency

7.4.2 CYP3A4 Inducers and Inhibitors

In vitro, MLN4924 (pevonedistat) is metabolized predominantly by CYP3A4 with a small contribution from CYP2D6. Based on drug-drug interaction study results, administration of MLN4924 (pevonedistat) with moderate and strong CYP3A inhibitors and P-gp inhibitors is permitted, while use of strong CYP3A inducers should be avoided. Strong inducers of CYP3A4 should be discontinued within 14 days prior to the first dose of MLN4924 (pevonedistat) and are prohibited for the duration of the study (see Appendix IX).

7.4.3

Concomitant administration of BCRP inhibitors (e.g., cyclosporine, eltrombopag) should be avoided, however, limited use is permitted if clinically necessary and no suitable alternative exists. In this case, a patient may receive the BCRP inhibitor from 24 hours after the last MLN4924 (pevonedistat) dose until 72 hours before the next MLN4924 (pevonedistat) dose.

7.4.4

Acetaminophen and acetaminophen-containing products may be used judiciously but should not exceed a dose of 37 mg/kg/day (maximum 2 g in 24 hours) on days MLN4924 (pevonedistat) is administered.

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. Bone marrow aspirate and/or biopsy, must be obtained within 14 days prior to start of protocol therapy. See Appendix VIII for Therapy Delivery Maps for each cycle.

STUDIES TO BE OBTAINED	Pre-Study	During Cycle 1	During Cycle 2
History	X	Weekly	X^
Physical Exam with vital signs[7]	X	Weekly	X^
Height, weight, BSA	X	Weekly	X^
Performance Status	X		
CBC, differential, platelets	X	Twice Weekly	X^
Pharmacokinetics[1]	X	X	
Electrolytes including Ca^{++}, PO_4, Mg^{++}	X	Weekly[6]	X^
Creatinine	X	Weekly	X^
ALT, AST, bilirubin (fractionated)[8]	X	Prior to each dose of MLN4924 (pevonedistat), then weekly	Prior to each dose of MLN4924 (pevonedistat), then weekly
Albumin	X		X^
Pregnancy Test[2]	X		X^
ECHO or gated radionuclide study	X	X[5]	X[5]
EKG	X	X[5]	X[5]
Bone Marrow Aspirate and/or biopsy	X	End of Cycle 1	End of Cycle 2
CSF for cell count, cytospin	X	End of Cycle 1	End of Cycle 2
PD (mRNA Transcript Levels)[3]		X	
PD (NEDDylated Protein Analysis)[4]		X	

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

1 See Section 8.2 for timing of PK studies.

2 Women of childbearing potential require a negative pregnancy test prior to starting Cycle 1 treatment and prior to Cycle 2; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control.

3 See Section 8.3 for timing of optional PD – mRNA Transcript Level studies.

4 See Section 8.4 for timing of optional PD – NEDDylated Protein Analysis studies.

5 Echo and EKG performed prior to Cycle 2 therapy (echo and EKG done at the end of Cycle 1 can count as long as it is done within 2 weeks prior to the start of Cycle 2 and before any subsequent therapy). An additional echo and EKG are to be obtained at the end of Cycle 2.

6 Monitor as clinically indicated for tumor lysis.

7 Vital signs should be checked prior to each MLN4924 (pevonedistat) infusion as well as at the end of treatment.

8 ALT, AST, and bilirubin tests must be performed and read prior to each dose of MLN4924 (pevonedistat).

8.2 Pharmacology (Required)

8.2.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of MLN4924 (pevonedistat) in children. Serum will be collected and MLN4924 (pevonedistat) concentration will be determined by a validated liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay. Samples will be analyzed by Covance Madison BioA.

8.2.2 Sampling Schedule (See Appendix IV-A and Appendix IV-B)

8.2.2.1 For patients ≤ 10 kg, blood samples will be obtained at the following time points during Cycle 1:

- Day 1: pre-dose, at the end of infusion, and at 4 – 6, and 24 hours after the end of infusion
- Day 5: pre-dose, at the end of infusion, and at 4 – 6, and 24 hours after the end of infusion

8.2.2.2 For patients > 10 kg, blood samples will be obtained at the following time points during Cycle 1:

- Day 1: pre-dose, at the end of infusion, and at 1, 2, 4, 6 – 8, and 24 hours after the end of infusion
- Day 3: pre-dose
- Day 5: pre-dose, at the end of infusion, and at 1, 2, 4, 6 – 8, 24, and 48 **OR** 72 hours after the end of infusion

8.2.3 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.

8.2.4 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.

8.2.5 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 (Appendix IV-A; Appendix IV-B), which must accompany the sample(s).

8.2.6 Sample Shipping Instructions
See Appendix XIII.

8.3 Pharmacodynamics - mRNA Transcript Levels (Optional)

8.3.1 Description of Studies and Assay
Peripheral blood will be collected from consenting patients to evaluate the effects of MLN4924 (pevonedistat) on mRNA transcript levels of genes that have been shown to be induced by MLN4924 (pevonedistat) mediated NAE inhibition. Samples will be analyzed by reverse transcription-polymerase chain reaction (RT-PCR) by Takeda Pharmaceuticals.

8.3.2 Sampling Schedule (See Appendix V)
Blood samples will be collected from consenting patients at the following time points during Cycle 1:

- Day 1: pre-dose
- Day 3 **OR** Day 5: 3 hours and 6 hours after the end of MLN4924 (pevonedistat) infusion (which is given after azacitidine)

8.3.3 Sample Collection and Handling Instructions
Blood samples (2 ml) will be collected in citrate vacutainer tubes at a site distant from the infusion in consenting patients. 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

1. Store at 4ºC until processed.
2. Ship in thermosafe box to address provided in Section 8.3.6.
   - 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

8.3.5 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 Correlative Study Form (Appendix V), 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 according to the lab manual.

8.4 Pharmacodynamics - NEDDylated Protein Analysis (Optional)

8.4.1 Description of Studies and Assay
Bone marrow and/or peripheral blood will be collected from consenting patients to examine NEDDylated protein degradation and to correlate it with MLN4924

(pevonedistat) response. Peripheral blood samples will only be collected from consenting patients with an initial absolute blast count ≥ 1000 blasts/µL (see Appendix VI-A for details). Bone marrow samples will be collected from consenting patients regardless of initial absolute blast count. Samples will be analyzed by reverse protein lysate array and immune-capillary electrophoresis.

8.4.2 Sampling Schedule (See Appendix VI-B and Appendix VII)

For questions about the sample delivery process, please contact Gaye Jenkins (gnjenkin@txch.org) or Dr. Terzah Horton (tmhorton@txch.org). Blood samples will only be collected from consenting patients with an initial absolute blast count ≥ 1000 blasts/µL (see Appendix VI-A for details). Blood samples will be collected from consenting patients at the following time points during Cycle 1:

- Day 1: prior to IV azacitidine and MLN4924 (pevonedistat) dose, 10 hours after the end of MLN4924 (pevonedistat) infusion, and 24 hours after the end of MLN4924 (pevonedistat) infusion
  - **NOTE:** The Day 1, Hour 0 sample can be obtained after the IT cytarabine dose.
- At the end of Cycle 1 on the same day as bone marrow evaluation.

Bone marrow aspirate will be collected from consenting patients at the following time points, regardless of initial absolute blast count:

- Pre-study on the same day as bone marrow evaluation
- At the end of Cycle 1 on the same day as bone marrow evaluation

8.4.3 Sample Collection and Handling Instructions

Blood samples will be collected in Cell Save tubes (3 ml) and heparinized tubes (2 ml). Samples may be collected from a central line. Either lithium heparin or sodium heparin is acceptable. Do NOT use lithium PST (plasma separator tubes). Record the exact time that the sample is drawn along with the exact time that the drug infusion begins. For end of Cycle 1 samples, drug infusion timing is not needed. See Appendix VI-A for detailed instructions.

Bone marrow samples (3 ml) will be collected in heparinized tubes or in COG shipping media. Record the exact time that the sample is drawn and whether the sample is a pre-study or end of Cycle 1 sample.

8.4.4 Sample Processing

Store samples in refrigerator until shipment.

8.4.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study number (ADVL1712), accession number, and the date and time the sample was drawn. Data should be recorded on the Correlative Study Forms (Appendix VI-B; Appendix VII), which must accompany the sample(s).

Please note the WBC and % blasts on the specimen transmittal form.

8.4.6 Sample Shipping Instructions

Ship the sample by Federal Express Priority Overnight delivery to:

Dr. Terzah Horton c/o Gaye Jenkins
Feigin Center, Suite 760.01
1102 Bates St.
Baylor College of Medicine
Houston, TX 77030
(832) 824-4676

Please email the Fed-Ex tracking number to the email addresses above and copy the ADVL1712 Research Coordinator on the email.

See Appendix VI-A for detailed shipping instructions.

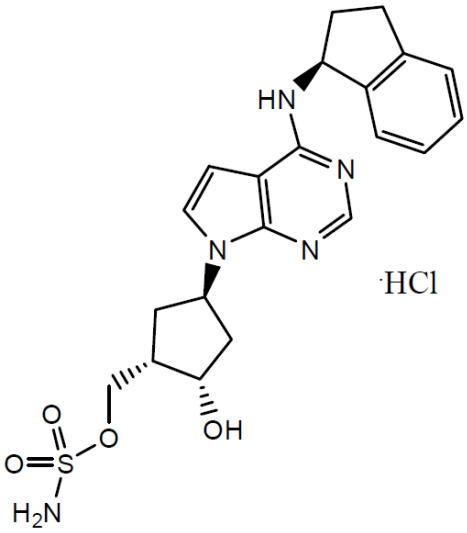
9.0 AGENT INFORMATION

9.1 MLN4924 (Pevonedistat) (08/15/20)

(TAK924, MLN4924-003 (hydrochloride salt), MLN4924-001 (free base), ML644507, ML00644807) NSC#793435

9.1.1 Structure and molecular weight

Molecular formula: $C_{21}H_{26}ClN_5O_4S$
Molecular weight: 443.52 (free base)
479.98 (hydrochloride salt)



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

9.1.2 Supplied by:

MLN4924 (pevonedistat) is supplied by Takeda Pharmaceuticals and distributed

by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

9.1.3 Formulation

The agent is supplied as a single-use 50 mg or 44 mg vial containing 10 mg/mL MLN4924 (pevonedistat) (free base, equivalent to 10.8 mg/mL MLN4924 [pevonedistat HCl]) in an aqueous solution of citric acid (anhydrous), trisodium citrate dihydrate, and Betadex Sulfobutyl Ether Sodium (Captisol®) at pH 3.3. Each USP Type I glass vial nominally contains 5 mL or 4.4 mL of compounded sterile solution, sealed with a fluoropolymer-coated butyl rubber stopper and oversealed with an aluminum seal and a plastic cap.

9.1.4 Storage

Vials of MLN4924 (pevonedistat) are to be kept dry and refrigerated at 2°-8°C (36° – 46° F) until dilution and use. Pevonedistat vials should be kept in their original carton until time of use. If original carton is not available, wrap vials in aluminum foil or similar light protective cover to protect from light. MLN4924 (pevonedistat) injection is stable at ambient temperature for 6 hours before dilution. Return vials to refrigerator if vial(s) are not to be used within 6 hours after removing from the refrigerator. All investigational supplies are to be kept in a secure area with controlled access.

If a storage temperature excursion is identified, promptly return MLN4924 (pevonedistat) to 2°-8°C (36° – 46° F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.5 Solution Preparation

To prepare the agent for administration dilute MLN4924 (pevonedistat) injection in 5% dextrose or 0.9% sodium chloride. The vial must not be shaken at any time during dose preparation. Before use, bring MLN4924 (pevonedistat) vials to ambient room temperature (15° – 30° C / 59° – 86° F). Do not use a water bath to warm up the vials.

MLN4924 (pevonedistat) is a cytotoxic anticancer drug. As with other potentially toxic compounds, caution should be exercised when handling MLN4924 (pevonedistat) injection. Refer to institutional guidelines regarding the proper handling and disposal of cytotoxic agents.

- The specified number of MLN4924 (pevonedistat) vials should be removed and allowed to equilibrate to room temperature prior to dilution. The vial must not be shaken at any time during dose preparation.
  For the pevonedistat packaged 10 vials per carton, two recommendations to protect the vial(s) from light (1 or 2 dispensed per cycle day) are:
  - Use a spare carton in the pharmacy and put the vial(s) in it
  - Wrap vial(s) in aluminum foil
- Using aseptic technique, the appropriate volume of drug should be withdrawn from vial(s), then injected into an IV bag containing 5% dextrose solution or 0.9% sodium chloride (QS to a final volume of 100 mL), and then gently inverted repeatedly to mix.

- For volume-restricted infants, a 20-fold dilution in 5% dextrose or 0.9% sodium chloride can be used to achieve the smallest possible volume. For example, to deliver 20 mg/m^2 dose of MLN4924 (pevonedistat) to an infant with a BSA of 0.5 m^2, withdraw 1 mL (10 mg) of MLN4924 (pevonedistat) solution from the vial and further dilute in 20 mL of 5% dextrose or 0.9% sodium chloride for administration.
- Inspect the prepared solution to ensure it is clear and free of visible particles.
- The MLN4924 (pevonedistat) prepared IV bag must be used within 6 hours (time to the end of an infusion) if stored at ambient temperature.
- The bag, needle, and syringe must be disposed of in a proper biohazard container.
- Use of non-DEHP IV bags, non-DEHP tubing with Teflon or polyurethane catheter and stainless steel needle, and non-DEHP solution set is preferred.

9.1.6 Stability

Stability studies are ongoing.

- The prepared IV solution is stable when stored at ambient room temperature up to 6 hours and must be administered within that time frame. Discard the IV bag if > 6 hours from the time of preparation.
- The prepared IV solution is stable when stored at 2^0 – 8^0 C (36^0 – 46^0 F) up to 18 hours. The IV solution can be brought to ambient room temperature before administering to patient, but must be used within 3 hours from the time it is removed from the refrigerator to completion of the IV infusion. Discard the IV bag if > 3 hours.

9.1.7 Administration

See Treatment and Dose Modification sections of the protocol.

MLN4924 (pevonedistat) will be administered intravenously over 60 minutes. MLN4924 (pevonedistat) should be administered through central or peripheral venous access. The use of in-line filter is NOT necessary for administration. Protecting IV bag from light during infusion is not required. The infusion may be slowed or stopped for any associated infusion-related reactions per institutional standards. All infusion times must be recorded. The total time from drug reconstitution to end of infusion must not exceed 6 hours. Doses of MLN4924 (pevonedistat) must be separated by at least 1 full calendar day. Infusion line should be flushed with 5% Dextrose or 0.9% sodium chloride immediately after IV administration is complete.

9.1.8 Potential drug interactions

Acetaminophen may be used judiciously but should not exceed a dose of 37 mg/kg/day (maximum 2 **g** in 24 hours) on days MLN4924 (pevonedistat) is administered.

In vitro, MLN4924 (pevonedistat) is metabolized via hydroxylation and oxidation, predominantly by CYP3A4 with a small contribution from CYP2D6 (approximately 3%). Based on drug-drug interaction study results, the administration of MLN4924 (pevonedistat) with moderate and strong CYP3A inhibitors and P-gp inhibitors is permitted, while the **use of strong CYP3A**

inducers should be avoided.

In vitro, MLN4924 (pevonedistat) does not inhibit the activities of CYP1A2, 2C9, 2C19, 2D6, and 3A4/5, but weakly and reversibly inhibits both CYP2B6 and 2C8; it does not induce CYP1A2, 2B6, and 3A4/5. Thus, MLN4924 (pevonedistat) is unlikely to affect the PK of drugs that are metabolized by these CYP450 isoforms.

MLN4924 (pevonedistat) is also a substrate for the drug efflux transporters, P-gp and BCRP, and a weak inhibitor of P-gp and BCRP-mediated transport. Additional in vitro transport studies showed that MLN4924 (pevonedistat) is not a substrate of the hepatic OATP, but it can inhibit OATP-mediated uptake of E3S and simvastatin and lovastatin. On the basis of these data and the recommended clinical dose range, MLN4924 (pevonedistat) is unlikely to affect the PK of other drugs that are known P-gp, BCRP, or OATP substrates, while the potential exists, albeit low, for drug interactions with BCRP inhibitors. Exclusion of P-gp inhibitors is not deemed warranted in clinical studies of MLN4924 (pevonedistat). However, the concomitant administration of BCRP inhibitors (e.g., cyclosporine, eltrombopag) should be avoided, however, limited use is permitted if clinically necessary and no suitable alternative exists. In this case, a patient may receive the BCRP inhibitor from 24 hours after the last MLN4924 (pevonedistat) dose until 72 hours before the next MLN4924 (pevonedistat) dose.

9.1.9 Patient Care Considerations

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] of 30 mL/min/1.73 m^2 or higher) based on the results of a population PK analysis. The effect of severe renal impairment (eGFR less than 30 mL/min/1.73 m^2) on MLN4924 (pevonedistat) PK has not been studied. Avoid use of MLN4924 (pevonedistat) in patients with severe renal impairment or end-stage renal disease.

The effect of hepatic impairment on MLN4924 (pevonedistat) PK has not been studied.

9.1.10 Toxicities

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

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

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple

investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.3, July 10, 2020[27]

Adverse Events with Possible Relationship to MLN4924 (Pevonedistat HCl) (CTCAE 5.0 Term) [n= 474]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
	Febrile neutropenia		***Febrile neutropenia (Gr 2)***
CARDIAC DISORDERS			
		Sinus tachycardia	
GASTROINTESTINAL DISORDERS			
	Abdominal distension		
	Abdominal pain		***Abdominal pain (Gr 2)***
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Mucositis oral		
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 2)***
Fever			***Fever (Gr 2)***
	Pain		***Pain (Gr 2)***
INFECTIONS AND INFESTATIONS			
	Lung infection		***Lung infection (Gr 2)***
	Upper respiratory infection		
	Urinary tract infection		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		***Bruising (Gr 2)***
INVESTIGATIONS			
Alanine aminotransferase increased			***Alanine aminotransferase increased (Gr 2)***
	Alkaline phosphatase increased		***Alkaline phosphatase increased (Gr 2)***
Aspartate aminotransferase increased			***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
	GGT increased		
	Platelet count decreased		***Platelet count decreased (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		
	Hypercalcemia		
	Hyperglycemia		
	Hypoalbuminemia		***Hypoalbuminemia (Gr 2)***

Adverse Events with Possible Relationship to MLN4924 (Pevonedistat HCl) (CTCAE 5.0 Term) [n= 474]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Hypocalcemia		
	Hypokalemia		***Hypokalemia (Gr 2)***
	Hypomagnesemia		***Hypomagnesemia (Gr 2)***
	Hyponatremia		
	Hypophosphatemia		***Hypophosphatemia (Gr 2)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Muscle cramp		***Muscle cramp (Gr 2)***
Myalgia			***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Headache		***Headache (Gr 2)***
	Nervous system disorders - Other (neuropathy peripheral, peripheral neuropathy)		
	Paresthesia		
PSYCHIATRIC DISORDERS			
	Anxiety		
	Confusion		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 2)***
	Epistaxis		
	Hypoxia		
	Pleural effusion		
	Productive cough		
	Respiratory, thoracic and mediastinal disorders - Other (rales)		
	Wheezing		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		
	Purpura		
VASCULAR DISORDERS			
	Hypotension		***Hypotension (Gr 2)***

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

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

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Cardiac arrest; Chest pain - cardiac; Heart failure; Myocarditis
EYE DISORDERS - Blurred vision
GASTROINTESTINAL DISORDERS - Ascites; Dyspepsia; Gastrointestinal disorders - Other (gastrointestinal necrosis); Gastrointestinal disorders - Other (gastrointestinal hemorrhage); Ileus; Small intestinal obstruction
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Generalized edema; Multi-organ failure; Non-cardiac chest pain
HEPATOBILIARY DISORDERS - Hepatic failure
INFECTIONS AND INFESTATIONS - Bacteremia; Sepsis; Sinusitis; Skin infection
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fall
INVESTIGATIONS - Investigations - Other (brain natriuretic peptide increased); Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hyperkalemia; Hyperuricemia
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Leukemia secondary to oncology chemotherapy; Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Intracranial hemorrhage; Spinal cord compression
PSYCHIATRIC DISORDERS - Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Dysuria; Renal and urinary disorders - Other (renal impairment); Urinary retention
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Nasal congestion; Oropharyngeal pain; Respiratory failure; Rhinorrhea
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Rash maculo-papular
VASCULAR DISORDERS - Hypertension; Phlebitis; Thromboembolic event

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

9.1.11 Agent Ordering and Agent Accountability

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

9.1.12 Clinical Drug Request

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers,

returns, or accountability call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

9.1.13 Agent Inventory Records

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

9.1.14 Investigator Brochure Availability

The current version(s) of the IB for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB coordinator via email.

9.1.15 Useful Links and Contacts

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

9.2 Azacitidine – Injection

(Vidaza®, 5-azacitidine) NSC# 102816 **(09/09/19)**

9.2.1 Source and Pharmacology

Azacitidine (4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one) is an analog of the naturally occurring pyrimidine nucleoside, cytidine. It differs from cytidine in having nitrogen in the 5-position of the heterocyclic ring. This substitution renders the ring chemically unstable and leads to rapid decomposition of the compound in

neutral or alkaline solution. Therefore, for SC or IV administration, the drug is supplied as a lyophilized powder to be reconstituted immediately prior to use.

Azacitidine was developed based on its strong in vitro and in vivo antileukemic activity at cytotoxic concentrations, and its differentiation-inducing potential at lower concentrations in hematopoietic and non-hematopoietic cell lines. The cytotoxic effects of azacitidine may be due to inhibition of protein synthesis and activation of DNA damage pathways, through incorporation into ribonucleic acid (RNA) and DNA, respectively. The ability of azacitidine to cause differentiation is attributed to its activity as a hypomethylating agent. Similar to cancer cells, the disturbed maturation of morphologically dysplastic hematopoietic cells in MDS is thought to reflect a block in their differentiation, resulting in accumulation of these precursors in the bone marrow in spite of low peripheral blood counts. This block in maturation (differentiation), with proliferation of preleukemic myeloblasts, provides a rationale for clinical trials of DNA methylation inhibitors (eg, azacitidine) in the treatment of MDS.

Pharmacokinetic studies using 14C-radiolabeled azacitidine to evaluate drug disposition demonstrated that azacitidine undergoes rapid and complete absorption following SC administration, with SC bioavailability greater than 70% and maximum concentration (Cmax) achieved 0.5 to 2 hours after dosing. The volume of distribution of azacitidine is 76 ± 26 L following IV administration. Its protein binding in human serum is low (< 10% bound). Azacitidine and/or its metabolites are cleared by the kidneys. The plasma elimination half-life (t1/2) is 3.4 to 6.2 hours and amount of radioactivity recovered in urine (50% to 98% of administered dose) were similar after IV and SC dosing.

In vitro and in vivo studies have demonstrated that spontaneous hydrolysis of azacitidine is the major pathway in different species, regardless of the route of administration. Azacitidine is not metabolized by cytochrome P450 isozymes (CYPs) and it will not produce clinically relevant PK drug-drug interactions due to CYP enzyme inhibition or induction when coadministered with CYP substrates, inducers, or inhibitors. Azacitidine is not a substrate for P-glycoprotein (P-gp) and is unlikely to produce any clinically relevant interactions as a P-gp substrate or an inhibitor.

9.2.2 Toxicity

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
Azacitidine (NSC 102816)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1800 patients.* Below is the CAEPR for Azacitidine.

Version 2.7, July 30, 2019[28]

Adverse Events with Possible Relationship to Azacitidine (CTCAE 5.0 Term) [n= 1800]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
	Febrile neutropenia	
CARDIAC DISORDERS		
	Heart failure	
	Pericardial effusion	
	Sinus tachycardia	
	Supraventricular tachycardia	
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
	Colitis	
Constipation		
Diarrhea		
	Esophagitis	
	Gastrointestinal hemorrhage[29]	
	Mucositis oral	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
Fever		
Injection site reaction		
IMMUNE SYSTEM DISORDERS		
		Allergic reaction
		Anaphylaxis
INFECTIONS AND INFESTATIONS		
Infection[30]		
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Bruising	
INVESTIGATIONS		
	Alanine aminotransferase increased	
	Alkaline phosphatase increased	
	Aspartate aminotransferase increased	
	Blood bilirubin increased	
	GGT increased	
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Acidosis	
	Anorexia	

Adverse Events with Possible Relationship to Azacitidine (CTCAE 5.0 Term) [n= 1800]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
	Hypokalemia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Generalized muscle weakness	
	Myalgia	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
	Peripheral motor neuropathy	
	Somnolence	
PSYCHIATRIC DISORDERS		
	Anxiety	
	Confusion	
	Insomnia	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Bronchopulmonary hemorrhage
	Cough	
	Dyspnea	
	Epistaxis	
	Pharyngolaryngeal pain	
	Postnasal drip	
	Respiratory, thoracic and mediastinal disorders - Other (abnormal breath sound)[31]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Alopecia	
	Pruritus	
	Purpura	
	Rash maculo-papular	
VASCULAR DISORDERS		
	Hematoma	
	Hypotension	

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

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal

hemorrhage under the GASTROINTESTINAL DISORDERS SOC.
[3]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.
[4]Abnormal breath sounds include rales and rhonchi.

Adverse events reported on azacitidine trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that azacitidine caused the adverse event:
BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (agranulocytosis); Blood and lymphatic system disorders - Other (lymphadenopathy); Blood and lymphatic system disorders - Other (pancytopenia); Blood and lymphatic system disorders - Other (splenomegaly); Blood and lymphatic system disorders - Other (transfusion: platelets); Bone marrow hypocellular; Hemolysis; Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiac valve vegetation); Cardiac disorders - Other (Wolff-Parkinson-White syndrome); Chest pain - cardiac; Myocardial infarction; Palpitations; Pericarditis; Restrictive cardiomyopathy; Sinus bradycardia; Ventricular fibrillation
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
EYE DISORDERS - Eye disorders - Other (eye/conjunctival hemorrhage); Eye disorders - Other (retina hemorrhage); Papilledema; Uveitis
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Duodenal ulcer; Dyspepsia; Dysphagia; Enterocolitis; Esophageal pain; Esophageal ulcer; Flatulence; Gastritis; Gastrointestinal disorders - Other (enteritis); Gastrointestinal disorders - Other (inguinal hernia, obstructive); Gastrointestinal disorders - Other (intestinal ischemia); Gastrointestinal disorders - Other (intussusception); Gastrointestinal pain; Hemorrhoids; Pancreatitis; Periodontal disease; Small intestinal obstruction; Visceral arterial ischemia
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Death NOS; Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (systemic inflammatory response syndrome); Generalized edema; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure; Hepatobiliary disorders - Other (bile duct stone); Hepatobiliary disorders - Other (hepatic cirrhosis)
IMMUNE SYSTEM DISORDERS - Autoimmune disorder; Immune system disorders - Other (GVHD)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Burn; Fall; Fracture; Hip fracture; Injury, poisoning and procedural complications - Other (excoriation); Injury, poisoning and procedural complications - Other (transfusion reaction); Postoperative hemorrhage; Wound dehiscence
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Blood lactate dehydrogenase increased; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (blood urea increased); Investigations - Other (cardiac murmur); Investigations - Other (coagulopathy); Investigations - Other (protein total decreased); Investigations - Other (thrombocytosis); Lipase increased; Lymphocyte count increased; Serum amylase increased
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperglycemia; Hyperkalemia; Hyperphosphatemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (gout exacerbation); Metabolism and nutrition disorders - Other (hypovolemia); Metabolism and nutrition disorders - Other (low carbon dioxide)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Chest wall pain; Flank pain; Muscle cramp; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (chondritis); Musculoskeletal and connective tissue disorder - Other (intervertebral disc protrusion); Musculoskeletal and connective tissue disorder - Other (musculoskeletal stiffness); Neck pain
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) -

Myelodysplastic syndrome; Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (colonic polyp, vaginal polyp); Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (metastases to central nervous system); Treatment related secondary malignancy
NERVOUS SYSTEM DISORDERS - Dysesthesia; Dysgeusia; Hydrocephalus; Intracranial hemorrhage; Lethargy; Memory impairment; Nervous system disorders - Other (head injury); Paresthesia; Peripheral sensory neuropathy; Seizure; Stroke; Syncope
PSYCHIATRIC DISORDERS - Delirium; Depression; Hallucinations; Psychiatric disorders - Other (mental status changes)
RENAL AND URINARY DISORDERS - Chronic kidney disease; Dysuria; Hematuria; Proteinuria; Renal and urinary disorders - Other (bladder distention); Renal and urinary disorders - Other (calculus urinary); Renal calculi; Urinary frequency; Urinary retention
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Erectile dysfunction; Reproductive system and breast disorders - Other (benign prostatic hyperplasia); Uterine hemorrhage; Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Atelectasis; Hypoxia; Laryngeal hemorrhage; Nasal congestion; Oropharyngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Pneumothorax; Productive cough; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (chronic obstructive pulmonary disease); Respiratory, thoracic and mediastinal disorders - Other (pharyngeal erythema); Rhinorrhea; Sinus pain; Wheezing
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Palmar-plantar erythrodysesthesia syndrome; Skin and subcutaneous tissue disorders - Other (skin laceration); Skin and subcutaneous tissue disorders - Other (skin lesion); Skin and subcutaneous tissue disorders - Other (skin nodule); Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Skin induration; Urticaria
VASCULAR DISORDERS - Flushing; Hypertension; Thromboembolic event; Vascular disorders - Other (pallor); Vascular disorders - Other (poor venous access); Vasculitis

Note: Azacitidine in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated.

9.2.3 Formulation and Stability

Azacitidine is supplied as lyophilized powder in 100 mg single-use vials without antibacterial preservatives. Store unreconstituted vials at 25° C (77° F); excursions permitted to 15°-30° C (59°-86° F).

For IV administration: Reconstitute vial with 10 mL SWFI to form a 10 mg/mL solution; vigorously shake or roll vial until solution is dissolved and clear. Mix in 50 to 100 mL of NS or lactated Ringer's injection for infusion. For infants and small children, azacitidine can be diluted in volumes less than 50 mL to a final concentration between 0.9 mg/mL and 4 mg/mL. The reconstituted product may be stored at 25° C (77° F), but the administration of the intravenous solution must be completed within 1 hour of reconstitution. **Solutions for IV administration have very limited stability and must be prepared immediately prior to each dose.**

Azacitidine is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions have the potential to increase the rate of degradation of azacitidine and should therefore be avoided.

9.2.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

IV: Infuse over 10 to 40 minutes. Infusion must be completed within 1 hour of vial reconstitution.

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

9.3 Cytarabine (07/13/15)

(Cytosine arabinoside, Ara-C, Cytosar®) NSC #63878

9.3.1 Source and Pharmacology

Cytarabine appears to act through the inhibition of DNA polymerase. A limited, but significant, incorporation of cytarabine into both DNA and RNA has also been reported. It exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and under certain conditions blocking the progression of cells from the G1 phase to the S-phase. Cytarabine is metabolized by deoxycytidine kinase and other nucleotide kinases to the nucleotide triphosphate (Ara-CTP), an effective inhibitor of DNA polymerase. Ara-CTP is inactivated by a pyrimidine nucleoside deaminase, which converts it to the nontoxic uracil derivative (Ara-U). It appears that the balance of kinase and deaminase levels may be an important factor in determining sensitivity or resistance of the cell to cytarabine. It has an initial distributive phase t½ of about 10 minutes, with a secondary elimination phase t½ of about 1 to 3 hours. Peak levels after intramuscular or subcutaneous administration of cytarabine occur about 20 to 60 minutes after injection and are lower than IV administration. Intrathecally administered doses are metabolized and eliminated more slowly with a t½ of about 2 hours.

9.3.2 Toxicity

Toxicity: (Intravenous, SubQ, IM)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, anorexia *With High Dose*: conjunctivitis	Flu-like symptoms with fever, rash	Ara-C syndrome (fever, myalgia, bone pain, occasionally chest pain, maculopapular rash, malaise, conjunctivitis), anaphylaxis, swelling, pain and redness at the site of the medication injection (SubQ or IM injection) *With High Dose:* cardiomyopathies (vasculitis, and pericarditis), cerebral and cerebellar dysfunction including: encephalopathy, aseptic meningitis, ataxia, dysphasia,

			nystagmus, a decreased level of consciousness, personality changes, somnolence, seizures
Prompt: Within 2-3 weeks, prior to the next course	Myelosuppression (anemia, thrombocytopenia, leukopenia, megaloblastosis, reticulocytopenia), stomatitis, alopecia	Diarrhea, hypokalemia, hypocalcemia, hyperuricemia *With High Dose*: capillary pulmonary leak syndrome (RDS, pulmonary edema)	Hepatotoxicity, sinusoidal obstruction syndrome (SOS, formerly VOD), urinary retention, renal dysfunction, pain and erythema of the palms and soles
Delayed: Any time later during therapy, excluding the above conditions			Asymptomatic nonoliguric rhabdomyolysis
Unknown Frequency and Timing:	Fetal toxicities and teratogenic effects of cytarabine have been noted in humans. It is unknown whether the drug is excreted in breast milk.		

Toxicity: (Intrathecal)

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoiditis	Rash, somnolence, meningismus, convulsions, paresis
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, ataxia
Delayed: Any time later during therapy, excluding the above condition			Necrotizing leukoencephalopathy, paraplegia, blindness (in combination with XRT & systemic therapy)

9.3.3 Formulation

Cytarabine for Injection is available in vials of 100 mg, 500 mg, 1 g, and 2 g containing a sterile powder for reconstitution. It is also available at a 20 mg/mL concentration with benzyl alcohol (25 mL per vial) or as a preservative free solution (5 mL, 50 mL per vial), and at a 100 mg/mL concentration with benzyl alcohol (20 mL vial) or as preservative free solution (20 mL vial). Hydrochloric acid and/or sodium hydroxide may be added to adjust the pH. Store at 25°C (77°F); excursions permitted to 15°-30°C (59° 86°F). Cytarabine solutions should be protected from light.

9.3.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

IV Infusion:

Reconstitute the lyophilized powder with Bacteriostatic Water for Injection or NS injection. Solution containing bacteriostatic agent should not be used for the preparation of doses > 200 mg/m^2. May be further diluted with dextrose or sodium chloride containing solutions. May give by IV push injection, by IV infusion, or by continuous infusion.

High Dose (≥ 1000 mg/m²/dose): Administer steroid eye drops (dexamethasone or prednisolone), 2 drops each eye q6h beginning immediately before the first dose and continuing 24 hours after the last dose. If patient does not tolerate steroid eye drops, administer artificial tears on a q2-4 hour schedule.

Stability: When reconstituted with Bacteriostatic Water for Injection, cytarabine is stable for 48 hours at room temperature. Solutions reconstituted without a preservative should be used immediately. Discard if solution appears hazy. Diluted solutions in D5W or NS are stable for 8 days at room temperature; however, the diluted cytarabine should be used within 24 hours for sterility concerns.

Intrathecal:
For intrathecal administration, dilute with 5-10 mL (or volume per institutional practice) preservative free 0.9% sodium chloride injection, lactated Ringer's injection, Elliot's B solution. The volume of CSF removed should be equal to at least ½ the volume delivered.

Patient Age (years)	Recommended volume	10% CSF volume	CSF Volume *
1 – 1.99	5 – 10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	5 – 10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	5 – 10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	5 – 10 mL	13 mL	130 ± 30 mL (adults)

**Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection; N Engl J Med. 1962 Dec 20; 267:1273-8*

Of Note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal cytarabine mixed in NS, lactated Ringer's injection, or Elliot's B solution is stable for 24 hours at 25ºC but contains no preservative and should be administered as soon as possible after preparation.

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

9.4 Fludarabine (01/10/18)

(Fludara®, fludarabine phosphate, 2-fluoro-ara-AMP) NSC# 312887

9.4.1 Source and Pharmacology:
Fludarabine phosphate is a synthetic purine nucleoside. It differs from the physiologic nucleosides, adenosine, in that the sugar moiety is arabinose instead of ribose, and by the addition of a fluorine atom to the purine base adenine. Fludarabine is also a fluorinated nucleotide analog the antiviral agent vidarabine, (ara-A). The addition of fluorine results in increased aqueous solubility and resistance to enzymatic degradation by adenosine deaminase. Fludarabine

(2-fluoro-ara-A) is commercially available as the monophosphate salt (2-fluoro-ara-AMP). The monophosphorylation increases the drug's aqueous solubility while maintaining pharmacologic activity. The chemical name for fludarabine phosphate is 9H-Purin-6-amine, 2-fluoro-9-(5-0-phosphono β-D-arabino-furanosyl) (2-fluoro-ara-AMP) and the molecular weight is 365.2.

Fludarabine is a purine antagonist antimetabolite. *In vivo*, fludarabine phosphate is rapidly dephosphorylated to 2-fluoro-ara-A and then it is phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2-fluoro-ara-ATP. This metabolite appears to act by inhibiting DNA polymerase alpha, ribonucleotide reductase and DNA primase, thus inhibiting DNA synthesis. The mechanism of action of this antimetabolite is not completely characterized and may be multi-faceted.

Phase I studies in humans have demonstrated that within several minutes after intravenous infusion, fludarabine phosphate is converted to the active metabolite, 2-fluoro-ara-A and becomes undetectable. Therefore, pharmacokinetics studies have focused on 2-fluoro-ara-A. Fludarabine phosphate 25 mg/m^2 infused intravenously over 30 minutes to adult cancer patients, showed a moderate accumulation of 2-fluoro-ara-A. During a 5-day treatment schedule, 2-fluoro-ara-A plasma trough levels increased by a factor of about 2.

Fludarabine is widely distributed. The volume of distribution at steady state (V_{ss}) reported after daily administration of 25 mg/m^2 for 5 days to adults averaged at 96-98 L/m^2. Tissue distribution studies in animals indicate that the highest concentrations of the drug are in liver, kidney, and spleen. Although the extent to which fludarabine and/or its metabolites distribute into the CNS in humans has not been determined to date, severe neurologic toxicity (e.g., blindness, coma) has been reported in patients receiving the drug, particularly in high dosages. There is evidence from animal studies that fludarabine distributes into the CNS and that a toxic metabolite (2-fluoroadenine, possibly formed by bacteria in the GI tract), can be absorbed systematically via enterohepatic circulation and distributed into CSF. According to *in vitro* data, about 19-29% of fludarabine is bound to plasma proteins.

Following IV administration, fludarabine phosphate is dephosphorylated rapidly to fludarabine. Plasma concentrations of fludarabine decline in a linear, dose-independent manner. The elimination profile of fludarabine also has been reported to be either biphasic or triphasic; however, reported terminal elimination half-lives have been similar. In adult cancer patients receiving fludarabine 25 mg/m^2 as a 30-minute IV infusion daily for 5 days, a terminal half-life of about 20 hours was reported. In a limited number of pediatric patients, the plasma concentration profile of fludarabine exhibited both monoexponential and biexponential decay, with a mean $t_{1/2}$ of 10.5 hours in patients with monoexponential elimination and a $t_{1/2}$ of 1.2-1.4 and 12.4-19 hours, respectively, in patients with biexponential elimination.

Renal clearance accounts for about 40% of the total body clearance of fludarabine. Renal elimination appears to become more important at high dosages of the drug. The dose of fludarabine needs to be adjusted in patients with moderate renal impairment.

The use of fludarabine in combination with pentostatin is not recommended due to the risk of severe pulmonary toxicity.

9.4.2 Toxicity:

	Common Happens to 21-100 subjects out of every 100	**Occasional** Happens to 5-20 subjects out of every 100	**Rare** Happens to < 5 subjects out of every 100
Immediate: Within 1-2 days of receiving drug	Fever, fatigue, weakness, pain, nausea, vomiting, anorexia, cough, dyspnea	Edema including peripheral edema, chills, rash, diarrhea, rhinitis, diaphoresis, malaise, abdominal pain, headache, back pain, myalgia, stomatitis, flu-like syndrome	Anaphylaxis, tumor lysis syndrome, dehydration*
Prompt: Within 2-3 weeks, prior to next course	Myelosuppression (anemia, neutropenia, thrombocytopenia), infection (urinary tract infection, herpes simplex infection, pneumonia, upper respiratory)	Weight loss, gastrointestinal bleeding, hemoptysis, paresthesia, allergic pneumonitis, bronchitis, pharyngitis, visual disturbance, hearing loss, hyperglycemia	Sinusitis, dysuria, opportunistic infections and reactivation of latent viral infections like Epstein-Barr virus (EBV), herpes zoster and John Cunningham (JC) virus (progressive multifocal leukoencephalopathy [PML])[L], EBV associated lymphoproliferative disorder, panycytopenia (can be prolonged), pulmonary hypersensitivity[a] (dyspnea, cough, hypoxia, interstitial pulmonary infiltrate), pulmonary toxicity (acute respiratory distress syndrome [ARDS], pulmonary fibrosis, pulmonary hemorrhage, respiratory distress, respiratory failure), pericardial effusion, skin toxicity (erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis, pemphigus), liver failure, renal failure, hemorrhage, transfusion-associated graft-versus-host disease has occurred following transfusion of nonirradiated blood products, phlebitis*, sleep disorder*, cerebellar syndrome*, depression*, mentation impaired*, alopecia*, pruritus*, seborrhea*, esophagitis*, constipation*, mucositis*, dysphagia*, hesitancy*, cholelithiasis*, abnormal liver function tests*, osteoporosis*, arthralgia*, abnormal renal function test*, proteinuria*, epistaxis*, hemorrhagic cystitis*, eosinophilia*
Delayed: Any time later during therapy, excluding the above conditions			Neurotoxicity (increased with high doses): seizures, agitation, confusion, weakness, visual disturbances, optic neuritis, optic neuropathy, photophobia, blindness, paralysis, coma, death, peripheral neuropathy[a]; autoimmune phenomena: thrombocytopenia/thrombocytopenic purpura

			(ITP), Evans syndrome, hemolytic anemia, acquired hemophilia
Late: Any time after completion of treatment			Myelodysplastic syndrome/acute myeloid leukemia (mainly associated with prior or concomitant or subsequent treatment with other anticancer treatments), skin cancer (new onset or exacerbation)
Unknown Frequency and Timing:	**Pregnancy Category D** Based on its mechanism of action, fludarabine phosphate can cause fetal harm when administered to a pregnant woman. Fludarabine phosphate was embryolethal and teratogenic in both rats and rabbits.		

(L) Toxicity may also occur later.
* Reported in ≤ 3% of subjects. Since these are not considered life threatening they are not included in the consent.
[a] These effects were not reported in children.

9.4.3 Formulation and Stability

Fludarabine phosphate injection is available as sterile lyophilized powder and in solution. Each single-dose vial of powder contains 50 mg of the active ingredient fludarabine phosphate, 50 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. After reconstitution, the pH range for the final product is 7.2-8.2. The single-dose solution vial contains 25 mg/mL, 2 mL of fludarabine phosphate. It may contain mannitol and is preservative-free.

Fludarabine phosphate vials should be stored refrigerated at 2-8ºC (36-46ºF).

9.4.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

Fludarabine phosphate powder should be reconstituted with 2 mL of Sterile Water for Injection. The solid cake should fully dissolve in 15 seconds or less. The resulting concentration is 25 mg/mL. When reconstituted to a final concentration of 25 mg/mL, the drug is stable for at least 16 days at room temperature and normal light conditions. The manufacturer recommends that the solution be used within 8 hours after reconstitution.

Prior to administration, fludarabine 25 mg/mL solution or the reconstituted 25 mg/mL solution should be further diluted in 100 mL or 125 mL of D5W or NS. Concentrations of 0.25 to 1 mg/mL have been used in clinical trials. When diluted to a final concentration of 1 mg/mL, fludarabine is stable for at least 16 days at room temperature and normal light conditions. The manufacturer recommends that the diluted solution be used within 8 hours after preparation. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.

9.4.5 Supplier:

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

9.5 Intrathecal Triples (Methotrexate/Hydrocortisone/Cytarabine, IT-3) (05/08/12)

9.5.1 Source and Pharmacology

The intrathecal route of administration of a drug produces more consistent CSF drug concentrations at relatively smaller doses because of the volume difference between the CSF and blood compartments (140 mL vs. 3500 mL in an adult). (The CSF volume of children after the first 3 years is equivalent to that of an adult). Drug half-lives are longer as well because clearance is related to flow rather than metabolism or protein binding. Intrathecal methotrexate has a biphasic elimination curve from the CSF with a $t_{½}$ of 4.5 and 14 hours respectively. Following IT injection of cytarabine the elimination of the drug from the CSF is biphasic with a $t_{½}$ of 1 and 3.4 hours respectively which is 8-fold longer than the clearance from plasma. The elimination of hydrocortisone is similarly prolonged.

9.5.2 Toxicity

Intrathecal Triple Therapy (Methotrexate/Hydrocortisone/Cytarabine) Toxicity:

	Common Happens to 21-100 children out of every 100	**Occasional** Happens to 5-20 children out of every 100	**Rare** Happens to < 5 children out of every 100
Immediate: Within 1-2 days of receiving drug	Nausea, vomiting, fever, headache	Arachnoditis: (headache, fever, vomiting, meningismus and pleocytosis)	Rash, anaphylaxis (L), paresis, bleeding into subarachnoid or subdural space (risk > with platelet counts <20,000), confusion, fatigue, disorientation, seizures
Prompt: Within 2-3 weeks, prior to the next course			Myelosuppression, somnolence, ataxia, cranial nerve palsy, transient and rarely permanent paraplegia (L), speech disorders
Delayed: Any time later during therapy, excluding the above condition		Cognitive disturbances (L), learning disabilities (L)	Demyelating leukoencephalopathy[1] (L), blindness[1]
Late: Any time after the completion of treatment			Progressive CNS deterioration[1]

[1] *May be enhanced by systemic therapy such as high dose methotrexate or cytarabine and/or cranial irradiation.*
(L) Toxicity may also occur later.

9.5.3 Formulation and Stability

Methotrexate 25 mg/mL preservative free 2 mL vial or methotrexate 20 mg preservative free sterile powder for injection vial. Cytarabine 100 mg preservative free sterile powder for injection. Hydrocortisone sodium succinate 100 mg vial sterile powder for injection.

9.5.4 Guidelines for Administration

See Treatment and Dose Modification sections of the protocol.

For intrathecal administration, dilute each agent with 5-10 mL preservative free NS, lactated ringers or Elliot's B solution or as per institutional standard of

practice. The volume of CSF removed should be equal to at least half the volume delivered.

Patient Age (years)	Doses (MTX/Hydrocortisone/Ara-C)	Recommended volume	10% CSF volume	CSF Volume *
0 – 0.99	7.5 mg / 7.5 mg / 15 mg	5-10 mL	5 mL	50 ± 10 mL (babies)
1 – 1.99	8 mg / 8 mg / 16 mg	5-10 mL	5 mL	50 ± 10 mL (babies)
2 – 2.99	10 mg / 10 mg / 20 mg	5-10 mL	8 mL	80 ± 20 mL (younger children)
3 – 8.99	12 mg / 12 mg / 24 mg	5-10 mL	10 mL	100 ± 20 mL (older children)
9 or greater	15 mg / 15 mg / 30 mg	5-10 mL	13 mL	130 ± 30 mL (adults)

**Rieselbach, R.E. et.al. Subarachnoid distribution of drugs after lumbar injection. N Engl J Med 1962 Dec 20; 267:1273-8*

Of note: Larger volumes approximating at least 10% of the CSF volume, isovolumetric delivery, with the patient remaining prone after the procedure may facilitate drug distribution. These procedures have not been validated in clinical trials. They are allowed but not mandated for patients on COG studies.

Intrathecal triples are stable in NS for 24 hours at 25ºC but contain no preservative and should be administered as soon as possible after preparation.

9.5.5 Supplier

Commercially available from various manufacturers. 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) Evidence of treatment failure (See Section 12.2.5).
b) Adverse Events requiring removal from protocol therapy (See Section 6).
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 2 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 MLN4924 (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) The patient does not receive protocol treatment after study enrollment.
c) Death
d) Lost to follow-up
e) Withdrawal of consent for any required observations or data submission.
f) Enrollment onto another COG therapeutic (anti-cancer) study

11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

11.1 Sample Size and Study Duration

A minimum of 4 and a maximum of 18 evaluable patients will be required to complete the dose confirmation part of the study using a rolling 6 design. Once the MTD or recommended Phase 2 dose has been defined, up to 6 additional patients may be enrolled to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). Therefore, a maximum of 23 patients are anticipated to be enrolled in this study allowing for two dose levels, PK expansion, and 20% inevaluability. Review of the enrollment rate into previous COG new agent studies indicates that 1-2 patients per month are available, which will permit completion of the study within 12-23 months.

In the unlikely event that two DLTs of different classes occur, then expansion to 12 patients at that dose level may be considered if ALL of the following conditions are met: 1) one of the DLTs does not appear to be dose and/or drug-related, 2) the Adverse Effects are readily reversible, 3) the study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable (see Section 11.2.2). In this case, the absolute maximum number of patients would be 38 patients allowing for 12 patients at each of two dose levels, 6 patients for PK expansion, and 20% inevaluability. This would be completed within 19-38 months.

Given the novelty of this regimen, enhanced monitoring for DLTs will be performed in the first 3 patients. If 2 DLTs are observed then the dose will be de-escalated to DL-1. If 1 DLT is observed in the first 2 patients then a period of 30 days must have elapsed between the first dose of MLN4924 (pevonedistat) in the 3rd patient prior to enrolling the 4th patient.

11.2 Definitions

11.2.1 Evaluable For Adverse Events

Any patient who receives at least 2/3 doses of MLN4924 (pevonedistat) during Cycle 1 or who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-confirmation portion during Cycle 1, patients must receive at least 85% of the prescribed dose 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 5.6) 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 and/or drug-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
- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the RP2D/MTD during the dose confirmation portion of the study. If ≥ 1/3 of the cohort of patients at the RP2D/MTD (during the dose confirmation plus the PK expansion) experience DLT then the MTD will be exceeded.

11.3 Dose Confirmation and Determination of MTD/RP2D

The rolling six phase 1 trial design will be used for the conduct of this study.[32] There is no dose escalation beyond DL1 (20 mg/m^2); but the R6 logic will be used to determine the MTD/RP2D. DL1 will be defined as the RP2D if there are less than or equal to 1 patient(s) with a DLT among up to six evaluable patients. Otherwise, DL-1 will open to accrual of up to six evaluable patients. DL-1 will be defined as the MTD/RP2D if there are less than or equal to 1 patient(s) with a DLT among six evaluable patients. Otherwise, DL-1 will have exceeded the MTD and the study will close to accrual without having defined an MTD/RP2D.
In addition to determination of the RP2D/MTD, a descriptive summary of all toxicities will be reported.

11.4 Inclusion of Children, Women and Minorities

PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	3	3	0	0	6
White	11	17	2	2	32
More Than One Race	0	0	0	0	0
Total	14	20	2	2	38

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.

11.5 Pharmacokinetic and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of MLN4924 (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 MLN4924 (pevonedistat), patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to criteria for patients with AML, 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 website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

12.2 Response Criteria for Patients with Leukemia

12.2.1 Complete Remission (CR)

Attainment of an M1 bone marrow (< 5% blasts and adequate marrow cellularity) with no evidence of circulating blasts or extramedullary disease and with recovery of peripheral blood counts (ANC ≥ 1000/uL and platelet count ≥ 100,000/uL). Flow cytometry may be useful to distinguish between leukemia and a regenerating bone marrow. There is no requirement for bone marrow cellularity.

12.2.2 Complete Remission with Partial Recovery of Platelet Count (CRp)

Attainment of an M1 bone marrow (< 5% blasts) and no evidence of circulating blasts or extramedullary disease and with recovery of ANC ≥ 1000/uL and platelet transfusion independence (defined as no platelet transfusions x 1 week).

12.2.3 Complete Remission with Incomplete Blood Count Recovery (CRi):

Attainment of an M1 bone marrow (<5% blasts) and no evidence of circulating blasts or extramedullary disease and with ANC < 1000/uL or platelet count < 100,000/uL without platelet transfusion independence (defined as no platelet transfusions x 1 week).

12.2.4 Partial Response

Attainment of M2 marrow status (≥ 5% or < 25% blasts cells and adequate cellularity) and at least 50% decrease in bone marrow blast percent from baseline. Bone marrow must have adequate cellularity (e.g. ≥ 10% if a biopsy is performed) to determine response. PR status will not be included in the calculation of response to the regimen. A repeat bone marrow aspiration within 14 days may be required to distinguish between a PR and increased blasts caused by bone marrow regeneration, and is left to the discretion of the investigator.

12.2.5 Treatment Failure

The definition of treatment failure includes:

A. An increase in the extent of bone marrow infiltration by leukemic cells (absolute increase of ≥ 20% blasts) OR
B. Development of extramedullary disease (EMD) OR
C. M2 marrow that does not qualify for PR status OR
D. An M1 marrow with circulating blasts OR
E. > 25% blasts in the bone marrow after Cycle 1 of therapy
F. Subjects who have persistent CNS disease despite 6 doses of IT cytarabine or IT triples

12.2.6 Relapse

Morphologic relapse after CR/CRp/CRi is defined as a reappearance of leukemic blasts in the peripheral blood or ≥ 5% blasts in the bone marrow not attributable to any other cause (e.g. bone marrow regeneration after therapy). In the setting of recent treatment, if there are no circulating blasts and the bone marrow contains 5-20% blasts, a repeat bone marrow performed at least a week later is necessary to distinguish relapse from bone marrow regeneration. Should flow cytometric or molecular analyses suggest relapse (by reappearance of similar immunophenotype or mutation to the original leukemia) in the presence of < 5% blasts or ≥ 5% blasts in a regenerating marrow, a repeat bone marrow performed at least a week later is necessary to confirm relapse by morphologic methods. In such instances, the date of recurrence is defined as the first date that more than 5% blasts were observed in the bone marrow. The reappearance or development of cytogenetically proven extramedullary disease also indicates relapse. Molecular and/or genetic relapse is characterized by reappearance of a cytogenetic or molecular abnormality.

12.2.7 Unevaluable:

Aplastic or severely hypocellular marrow. In this instance, marrow evaluation should be repeated weekly until response determination can be made through at least Day 60.

12.2.8 Bone Marrow Classification:

M1 is < 5% blasts
M2 is 5-25% blasts
M3 is > 25% blasts

12.3 CNS Leukemia at Diagnosis

CNS 1:	In cerebral spinal fluid (CSF), absence of blasts on cytospin preparation, regardless of the number of WBCs.
CNS 2:	In CSF, presence < 5/μL WBCs and cytospin positive for blasts, or ≥ 5/μL WBCs but negative by Steinherz/Bleyer algorithm:
CNS 2a:	< 10/μL RBCs; < 5/μL WBCs and cytospin positive for blasts;
CNS 2b:	≥ 10/μL RBCs; < 5/μL WBCs and cytospin positive for blasts;
CNS 2c:	≥ 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts but negative by Steinherz/Bleyer algorithm (see below).
CNS 3:	In CSF, presence of ≥ 5/μL WBCs and cytospin positive for blasts and/or clinical signs of CNS leukemia:
CNS 3a:	< 10/μL RBCs; ≥ 5/μL WBCs and cytospin positive for blasts;
CNS 3b:	≥ 10/μL RBCs, ≥ 5/μL WBCs and positive by Steinherz/Bleyer algorithm (see below);
CNS 3c:	Clinical signs of CNS leukemia (such as facial nerve palsy, brain/eye involvement or hypothalamic syndrome).

Method of Evaluating Initial Traumatic Lumbar Punctures:

If the patient has leukemic cells in the peripheral blood and the lumbar puncture is traumatic and contains ≥ 5 WBC/μL and blasts, the following algorithm should be used to distinguish between CNS 2 and CNS 3 disease:

$$\frac{\text{CSF WBC}}{\text{CSF RBC}} > 2X \frac{\text{Blood WBC}}{\text{Blood RBC}}$$

A patient with CSF WBC ≥ 5/μL blasts, whose CSF WBC/RBC is 2X greater than the blood WBC/RBC ratio, has CNS disease at diagnosis. Example: CSF WBC = 60/μL; CSF RBC = 1500/μL; blood WBC = 46000/μL; blood RBC = 3.0 X 10^6/μL:

$$\frac{60}{1{,}500} = 0.04 > 2X \frac{46{,}000}{3.0 \times 10^6} = 0.015$$

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. The descriptions and grading scales found in the revised CTCAE version 5.0 will be used for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm).

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 in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported 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.

Effective Date: May 5, 2011

- 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.

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.

- 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.
- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.9 of the protocol.
- Grade 1-4 myelosuppression (anemia, thrombocytopenia, neutropenia) do not require expedited reporting
- Grade 1-2 AST/ALT elevations do not require expedited reporting

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 (telephone CTEP at: **301-897-7497** 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 to the NCI by fax (fax# 301-897-7404) and by email to the ADVL1712 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 to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP) 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 Data and Safety Monitoring Plan

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

13.7.1 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 developmental therapy 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 Developmental Therapeutics 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.

13.7.2 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 Developmental Therapeutics Chair, Vice Chair and Statistician on a weekly conference call.

13.8 **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 ADVL1712 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.

13.8.1 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 **Grade 3** ***"Pregnancy, puerperium and perinatal conditions - Other (Pregnancy)"*** under the ***"Pregnancy, puerperium and perinatal conditions"*** SOC.

- 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.

13.8.2 Pregnancy Loss (Fetal Death)

- Pregnancy loss is defined in CTCAE 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 recognizes any Grade 5 event as a patient death.

13.8.3 Death Neonatal

- Neonatal death, defined in CTCAE 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.**

- Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

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. If the baby is born with a birth defect or other anomaly, then a second CTEP-AERS report is required.

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. Reports are due January 31, April 30, July 31 and October 31. This is not a responsibility of institutions participating in this trial. Instructions for submitting data using the CDUS can be found on the CTEP web site: http://ctep.cancer.gov/reporting/cdus.html

14.3 CRADA/CTA/CSA

Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be

sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

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

14.4 Data and Safety Monitoring Plan

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

14.4.1 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.

14.4.2 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.

REFERENCES

1. Sarantopoulos J, Shapiro GI, Cohen RB, et al: Phase I Study of the Investigational NEDD8-Activating Enzyme Inhibitor Pevonedistat (TAK-924/MLN4924) in Patients with Advanced Solid Tumors. Clin Cancer Res 22:847-57, 2016
2. Soucy TA, Smith PG, Milhollen MA, et al: An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. Nature 458:732-6, 2009
3. Lin JJ, Milhollen MA, Smith PG, et al: NEDD8-targeting drug MLN4924 elicits DNA rereplication by stabilizing Cdt1 in S phase, triggering checkpoint activation, apoptosis, and senescence in cancer cells. Cancer Res 70:10310-20, 2010
4. Erba HP, Maris MB, Swords RT, et al: MLN4924, a Novel Investigational Inhibitor Of NEDD8-Activating Enzyme (NAE), In Adult Patients With Acute Myeloid Leukemia (AML) and Myelodysplastic Syndrome (MDS): Results From Multiple Dosing Schedules In a Phase 1 Study. Blood 122:1443-1443, 2013
5. Smith MA, Maris JM, Gorlick R, et al: Initial testing of the investigational NEDD8-activating enzyme inhibitor MLN4924 by the pediatric preclinical testing program. Pediatr Blood Cancer 59:246-53, 2012
6. Swords RT, Coutre S, Maris MB, et al: Results of a Clinical Study of Pevonedistat (Pev), a First-in-Class NEDD8-Activating Enzyme (NAE) Inhibitor, Combined with Azacitidine (Aza) in Older Patients (Pts) with Acute Myeloid Leukemia (AML). Blood 128:98-98, 2016
7. Swords RT, Erba HP, DeAngelo DJ, et al: Pevonedistat (MLN4924), a First-in-Class NEDD8-activating enzyme inhibitor, in patients with acute myeloid leukaemia and myelodysplastic syndromes: a phase 1 study. Br J Haematol 169:534-43, 2015
8. Kaspers GJ, Zimmermann M, Reinhardt D, et al: Improved outcome in pediatric relapsed acute myeloid leukemia: results of a randomized trial on liposomal daunorubicin by the International BFM Study Group. J Clin Oncol 31:599-607, 2013
9. Bhatla T, Wang J, Morrison DJ, et al: Epigenetic reprogramming reverses the relapse-specific gene expression signature and restores chemosensitivity in childhood B-lymphoblastic leukemia. Blood 119:5201-10, 2012
10. Bullinger L, Ehrich M, Dohner K, et al: Quantitative DNA methylation predicts survival in adult acute myeloid leukemia. Blood 115:636-42, 2010
11. Khan R, Schmidt-Mende J, Karimi M, et al: Hypomethylation and apoptosis in 5-azacytidine-treated myeloid cells. Exp Hematol 36:149-57, 2008
12. Murakami T, Li X, Gong J, et al: Induction of apoptosis by 5-azacytidine: drug concentration-dependent differences in cell cycle specificity. Cancer Res 55:3093-8, 1995
13. Yang X, Han H, De Carvalho DD, et al: Gene body methylation can alter gene expression and is a therapeutic target in cancer. Cancer Cell 26:577-590, 2014
14. Avramis VI, Mecum RA, Nyce J, et al: Pharmacodynamic and DNA methylation studies of high-dose 1-beta-D-arabinofuranosyl cytosine before and after in vivo 5-azacytidine treatment in pediatric patients with refractory acute lymphocytic leukemia. Cancer Chemother Pharmacol 24:203-10, 1989
15. Sun W, Triche T, Jr., Malvar J, et al: A phase 1 study of azacitidine combined with chemotherapy in childhood leukemia: a report from the TACL consortium. Blood 131:1145-1148, 2018
16. Czuczman NM, Barth MJ, Gu J, et al: Pevonedistat, a NEDD8-activating enzyme inhibitor, is active in mantle cell lymphoma and enhances rituximab activity in vivo. Blood 127:1128-37, 2016
17. Swords RT, Kelly KR, Smith PG, et al: Inhibition of NEDD8-activating enzyme: a novel approach for the treatment of acute myeloid leukemia. Blood 115:3796-800, 2010
18. Nawrocki ST, Kelly KR, Smith PG, et al: The NEDD8-activating enzyme inhibitor MLN4924 disrupts nucleotide metabolism and augments the efficacy of cytarabine. Clin Cancer Res 21:439-47, 2015
19. Visconte V, Nawrocki ST, Espitia CM, et al: Comprehensive quantitative proteomic profiling of

the pharmacodynamic changes induced by MLN4924 in acute myeloid leukemia cells establishes rationale for its combination with azacitidine. Leukemia 30:1190-4, 2016

20. Investigator's Brochure Pevonedistat (TAK-924/MLN4924), (ed 9), Millennium Pharmaceuticals, Inc., 2017
21. Swords RT, Watts J, Erba HP, et al: Expanded safety analysis of pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, in patients with acute myeloid leukemia and myelodysplastic syndromes. Blood Cancer J 7:e520, 2017
22. Iuvone L, Mariotti P, Colosimo C, et al: Long-term cognitive outcome, brain computed tomography scan, and magnetic resonance imaging in children cured for acute lymphoblastic leukemia. . Cancer 95(12):2562-70, 2002
23. Swords RT, Coutre S, Maris MB, et al: Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. Blood 131:1415-1424, 2018
24. Swords RT, Savona MR, Maris MB, et al: Pevonedistat (MLN4924), an Investigational, First-in-Class NAE Inhibitor, in Combination with Azacitidine in Elderly Patients with Acute Myeloid Leukemia (AML) Considered Unfit for Conventional Chemotherapy: Updated Results from the Phase 1 C15009 Trial. Blood 124:2313-2313, 2014
25. Smith GA, Damon LE, Rugo HS, et al: High-dose cytarabine dose modification reduces the incidence of neurotoxicity in patients with renal insufficiency. J Clin Oncol 15:833-9, 1997
26. Bennett WM, Aronoff GR, Morrison G, et al: Drug prescribing in renal failure: dosing guidelines for adults. Am J Kidney Dis 3:155-93, 1983
27. This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.,
28. Soldi R, Horrigan SK, Cholody MW, et al: Design, Synthesis, and Biological Evaluation of a Series of Anthracene-9,10-dione Dioxime beta-Catenin Pathway Inhibitors. J Med Chem 58:5854-62, 2015
29. Savvidou I, Khong T, Cuddihy A, et al: beta-Catenin Inhibitor BC2059 Is Efficacious as Monotherapy or in Combination with Proteasome Inhibitor Bortezomib in Multiple Myeloma. Mol Cancer Ther 16:1765-1778, 2017
30. Nomura M, Rainusso N, Lee YC, et al: Tegavivint and the beta-catenin/ALDH Axis in Chemotherapy-Resistant and Metastatic Osteosarcoma. J Natl Cancer Inst, 2019
31. Varghese S, Braggio DA, Gillespie J, et al: TGF-beta and CTGF are Mitogenic Output Mediators of Wnt/beta-Catenin Signaling in Desmoid Fibromatosis. Appl Immunohistochem Mol Morphol 25:559-565, 2017
32. Skolnik JM, Barrett JS, Jayaraman B, et al: Shortening the timeline of pediatric phase I trials: the rolling six design. J Clin Oncol 26:190-5, 2008
33. The Criteria Committee of New York Heart Association: Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels (ed 9). Boston, MA, Little, Brown & Co, 1994 pp. 253-256

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

FOR PATIENTS ≤ 10 KG:

Correlative Study	Appx.	Volume per Sample	Total Volume	Tube Type
Pharmacokinetics Study	IV-A	3 ml	24 ml	Vacutainer Tubes
Pharmacodynamics (mRNA Transcript Levels)	V	2 ml	6 ml	Citrate Vacutainer Tubes
Pharmacodynamics (NEDDylated Protein Analysis) – Blood Samples	VI	5 ml	20 ml	Cell Save Tubes and Heparinized Tubes
Pharmacodynamics (NEDDylated Protein Analysis) – Bone Marrow Samples	VII	3 ml	6 ml	Heparinized Tubes
		Total Blood + Bone Marrow Volume	**56 ml**	

FOR PATIENTS > 10 KG:

Correlative Study	Appx.	Volume per Sample	Total Volume	Tube Type
Pharmacokinetics Study	IV-B	3 ml	48 ml	Vacutainer Tubes
Pharmacodynamics (mRNA Transcript Levels)	V	2 ml	6 ml	Citrate Vacutainer Tubes
Pharmacodynamics (NEDDylated Protein Analysis) – Blood Samples	VI	5 ml	20 ml	Cell Save Tubes and Heparinized Tubes
Pharmacodynamics (NEDDylated Protein Analysis) – Bone Marrow Samples	VII	3 ml	6 ml	Heparinized Tubes
		Total Blood + Bone Marrow Volume	**80 ml**	

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 SGPT 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 SGOT 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

APPENDIX IV-A: PHARMACOKINETIC STUDY FORM FOR PATIENTS ≤ 10 KG

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

MLN4924 (Pevonedistat) Dose Level: _____mg/m^2 MLN4924 (Pevonedistat) Total Daily Dose: _____mg

Blood samples (3 ml) will be collected in chilled Becton-Dickinson Vacutainer K2 EDTA tubes at the following time points during Cycle 1 (± 10 min): Day 1 (pre-dose, at the end of MLN4924 [pevonedistat] infusion, and at 4 – 6 hrs, and 24 hrs after the end of MLN4924 [pevonedistat] infusion), and Day 5 (pre-dose, at the end of MLN4924 [pevonedistat] infusion, and at 4 – 6 hrs, and 24 hrs after the end of MLN4924 [pevonedistat] infusion).

Record the exact time the sample is drawn along with the exact time MLN4924 [pevonedistat] infusion begins and ends on Days 1 and 5.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to MLN4924 infusion	___/___/___	|__|__| : |__|__|
MLN4924 Dose on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|				
2	**Day 1**	At the end of MLN4924 infusion	___/___/___	|__|__| : |__|__|
3	**Day 1**	4 – 6 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
4	**Day 1**	24 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
5	**Day 5**	Prior to MLN4924 infusion	___/___/___	|__|__| : |__|__|
MLN4924 Dose on Day 5 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|				
6	**Day 5**	At the end of MLN4924 infusion	___/___/___	|__|__| : |__|__|
7	**Day 5**	4 – 6 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
8	**Day 5**	24 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.2.6. See Section 8.2 for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date:_____
(site personnel who collected samples)

APPENDIX IV-B: PHARMACOKINETIC STUDY FORM FOR PATIENTS > 10 KG

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

MLN4924 (Pevonedistat) Dose Level: _____mg/m^2 MLN4924 (Pevonedistat) Total Daily Dose: _____mg

Blood samples (3 ml) will be collected in chilled Becton-Dickinson Vacutainer K2 EDTA tubes at the following time points during Cycle 1 (± 10 min): Day 1 (pre-dose, at the end of MLN4924 [pevonedistat] infusion, and at 1 hr, 2 hrs, 4 hrs, 6 – 8 hrs, and 24 hrs after the end of MLN4924 [pevonedistat] infusion), Day 3 (pre-dose), and Day 5 (pre-dose, at the end of MLN4924 [pevonedistat] infusion, and at 1 hr, 2 hrs, 4 hrs, 6 – 8 hrs, and 24 hrs after the end of MLN4924 [pevonedistat] infusion, as well as at 48 **OR** 72 hours after the end of MLN4924 [pevonedistat] infusion).

Record the exact time the sample is drawn along with the exact time MLN4924 (pevonedistat) infusion begins and ends on Days 1, 3, and 5.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to MLN4924 infusion	___/___/___	|__|__| : |__|__|
MLN4924 Dose on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|				
2	**Day 1**	At the end of MLN4924 infusion	___/___/___	|__|__| : |__|__|
3	**Day 1**	1 hr after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
4	**Day 1**	2 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
5	**Day 1**	4 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
6	**Day 1**	6 – 8 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
7	**Day 1**	24 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
8	**Day 3**	Prior to MLN4924 infusion	___/___/___	|__|__| : |__|__|
MLN4924 Dose on Day 3 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|				
9	**Day 5**	Prior to MLN4924 infusion	___/___/___	|__|__| : |__|__|
MLN4924 Dose on Day 5 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|				
10	**Day 5**	At the end of MLN4924 infusion	___/___/___	|__|__| : |__|__|
11	**Day 5**	1 hr after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
12	**Day 5**	2 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
13	**Day 5**	4 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
14	**Day 5**	6 – 8 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
15	**Day 5**	24 hrs after MLN4924 infusion end time	___/___/___	|__|__| : |__|__|
16	**Day 5**	48 hrs after MLN4924 infusion end time*	___/___/___	|__|__| : |__|__|
17	**Day 5**	72 hrs after MLN4924 infusion end time*	___/___/___	|__|__| : |__|__|

*Blood samples are to be drawn 48 hours **OR** 72 hours after the Day 5 MLN4924 (pevonedistat) infusion end time. Do not collect blood for both timepoints.

One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. A second copy should be sent with the samples to the address listed in Section 8.2.6. See Section 8.2 for detailed guidelines for packaging and shipping PK samples.

Signature: _____ Date:_____
(site personnel who collected samples)

APPENDIX V: PHARMACODYNAMICS (MRNA TRANSCRIPT LEVELS) 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

MLN4924 (Pevonedistat) Dose Level: _____mg/m^2 MLN4924 (Pevonedistat) Total Daily Dose: _____mg

In consenting patients, blood samples (2 ml) will be collected in citrate vacutainer tubes at the following time points during Cycle 1 (± 10 min): Day 1 (pre-dose) and Day 3 **OR** Day 5 (3 hrs and 6 hrs after the end of MLN4924 [pevonedistat] infusion).

Record the exact time the sample is drawn along with the exact time MLN4924 (pevonedistat) infusion begins and ends on Day 1 and Day 3 **OR** 5.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to MLN4924 dose	___/___/__	|__|__| : |__|__|
MLN4924 Dose on Day 1 Date:___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|	
MLN4924 Dose on Day 3* Date:___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|	
2	**Day 3***	3 hrs after MLN4924 infusion end time	___/___/__	|__|__| : |__|__|
3	**Day 3***	6 hrs after MLN4924 infusion end time	___/___/__	|__|__| : |__|__|
MLN4924 Dose on Day 5* Date:___/___/___			**Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|	
2	**Day 5***	3 hrs after MLN4924 infusion end time	___/___/__	|__|__| : |__|__|
3	**Day 5***	6 hrs after MLN4924 infusion end time	___/___/__	|__|__| : |__|__|

*Blood samples are to be drawn on Day 3 **OR** Day 5, not on both days.

One copy of this Pharmacodynamic 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 Section 8.3 for detailed guidelines for packaging and shipping PD – mRNA Transcript Level samples.

Signature: _____ Date:_____
(site personnel who collected samples)

APPENDIX VI-A: PHARMACODYNAMICS (NEDDYLATED PROTEIN ANALYSIS) STUDY BLOOD SAMPLE INSTRUCTIONS

Eligible samples:

Samples should be sent to the Horton lab only if the patient samples meet the following criteria:

1) Eligible patients must have an initial absolute blast count of at least 1000 blasts/µL. To calculate the absolute blast percentage, multiply the total WBC by the % peripheral blasts:

(WBC)(% blast)(1000) = absolute blast count/µL

As an example, if the patient has a WBC of 10 and 50% blasts, the absolute blast count is:

(10)(.5)(1000) = 5000/µL

If the initial % blasts is unknown, send samples only if the total WBC is more than 10 and notify the Horton lab of the % blast as soon as available (contact info provided below). Sample can be batched, but must be received by the Horton lab no later than 72h after collection.

Note: Do not collect NEDDylated Protein Analysis samples if minimal residual disease is < 1%.

Sample collection time points:

	Day 1, Hour 0	Day 1, Hour 10	Day 1, Hour 24	End of Cycle 1
Peripheral Blood	5 mL total* (before start of IV azacitidine and MLN4924 [pevonedistat] infusion)** • 3 mL Cell Save • 2 mL heparin	5 mL total* (10h following completion of MLN4924 [pevonedistat] infusion) • 3 mL Cell Save • 2 mL heparin	5 mL total* (24h following completion of MLN4924 [pevonedistat] infusion) • 3 mL Cell Save • 2 mL heparin	5 mL total* (same day as bone marrow evaluation) • 3 mL Cell Save 2 mL heparin

*Sample Collection: Collect sample in syringe and send samples in Cell Save tubes (3 mL) and heparin tubes (2 mL). Either lithium heparin or sodium heparin is acceptable. **Do NOT use lithium PST (plasma separator tubes).** Cell Save tubes should have been received upon study activation by the lead CRA at your site. If Cell Save tubes are not available, the 5 mL can be sent in Heparin collection tubes. Do NOT send only Cell Save tubes as the proteasome and NF-kB analyses can be done only in heparin tubes.
**It is permissible to collect the Day 1, Hour 0 sample after the intrathecal cytarabine dose.

Shipping Note: Samples collected on Friday, Saturday and Sunday can be shipped Monday for Tuesday arrival.

Specimen Requirements:

- Store samples in refrigerator until shipment.
- Cell Save tubes will be provided by the Horton lab to each institution upon IRB approval.

- To obtain more Cell Save tubes, contact the Horton lab at the numbers provided below.
- If the Cell Save tubes are not available, submit entire 5 mL sample in heparin tubes. **Note that the sample integrity is greatly enhanced by the use of Cell Save tubes for 3 mL of the 5 mL material collected.**
- Each sample should be clearly labeled to include the study number (ADVL1712) as well as the treatment ID number and the accession number; along with date and time sample was drawn.
- Please note the WBC and % blasts on the specimen transmittal form below.
- The institutional immunophenotype report should be FAXed to 832-825-1206 (or e-mailed) and sent attn.: Gaye Jenkins c/o Horton laboratory. This is a secure FAX and is used only by laboratory personnel. **NOTE:** it is acceptable for blood to be collected from a central line.

Shipping Requirements:
Prior to sample collection, please contact Dr. Horton at (832) 824-4269 or Gaye Jenkins/Horton lab at (832) 824-4676 for instructions on shipping. Samples should be shipped in a box with a thick styrofoam container (NO clinic-packs). These containers can be found in your pathology department and are frequently received when your department receives antibody shipments. If you do not have access to these storage containers, a Thermo-safe box can be mailed to your site by regular mail. Please contact us before a patient is ready to enroll if you require a box for sample shipment. Shipment of boxes/tubes takes 5-7 business days and will be sent by USPS.

If Thermo-Safe shipping container is not available:

- Place collection tubes in a primary container. Wrap each collection tube separately to protect from breakage during shipment. Place the container in a thick Styrofoam box.
- Please place an **ice pack** around the primary container. During the non-winter months (year round except Christmas Day in Texas) (other parts of the country: April-October) add **additional ice packs** to the Styrofoam box to assure the samples stays cold during shipment.
- Package sample as appropriate for biologic material.

For all samples, including those in ThermoSafe containers:

- **Include ice packs in the ThermoSafe container in the space provided.**
- Include a copy of the Specimen Transmittal Form with each shipment.
- **If possible, please FAX the bone marrow immunophenotype report with the first peripheral blood sample.** If this is not possible, please send the report that day via fax (832 825-1206) or email to Dr. Horton at tmhorton@txch.org and Gaye Jenkins at gnjenkin@txch.org (Please strip HPI identifiers)
- **Ship the sample by Federal Express Priority Overnight delivery to:**

Dr. Terzah Horton c/o Gaye Jenkins
Feigin Center, Suite 760.01
1102 Bates St.
Baylor College of Medicine
Houston, TX 77030
832-824-4676

Courier information:

- Notify Gaye Jenkins or Horton lab representative prior to shipment of the sample. Phone: (832) 824-4676. Please email the Fed-Ex tracking number to the email addresses above.
  If possible, do not ship samples for delivery on a weekend or holiday. Weekend samples can be mailed Monday for Tuesday delivery.

APPENDIX VI-B: PHARMACODYNAMICS (NEDDYLATED PROTEIN ANALYSIS) STUDY FORM – BLOOD SAMPLES

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

MLN4924 (Pevonedistat) Dose Level: _____mg/m^2 MLN4924 (Pevonedistat) Total Daily Dose: _____mg

WBC: _____ /μL % Blasts: _____ %

In consenting patients, blood samples (5 ml) will be collected in Cell Save tubes (3 ml) and heparinized tubes (2 ml) at the following time points during Cycle 1 (± 10 min): Day 1 (prior to IV azacitidine and MLN4924 [pevonedistat] dose, 10 hrs after the end of MLN4924 [pevonedistat] infusion, and 24 hrs after the end of MLN4924 [pevonedistat] infusion), and at the end of Cycle 1 on the same day as bone marrow evaluation.

Record the exact time the sample is drawn along with the exact time MLN4924 (pevonedistat) infusion begins and ends on Day 1.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Day 1**	Prior to MLN4924 dose	___/___/__	|__|__| : |__|__|
MLN4924 Dose on Day 1 Date:___/___/___ **Infusion Start Time:** |__|__| : |__|__| **Infusion Stop Time:** |__|__| : |__|__|				
2	**Day 1**	10 hrs after MLN4924 infusion end time	___/___/__	|__|__| : |__|__|
3	**Day 1**	24 hrs after MLN4924 infusion end time	___/___/__	|__|__| : |__|__|
4	**End of Cycle 1**	Same day as bone marrow evaluation	___/___/__	|__|__| : |__|__|

One copy of this Pharmacodynamic 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 – mRNA Transcript Level samples.

Signature: _____ Date:_____
(site personnel who collected samples)

APPENDIX VII: PHARMACODYNAMICS (NEDDYLATED PROTEIN ANALYSIS) STUDY FORM – BONE MARROW SAMPLES

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

MLN4924 (Pevonedistat) Dose Level: _____mg/m^2 MLN4924 (Pevonedistat) Total Daily Dose: _____mg

WBC: _____ /µL % Blasts: _____ %

In consenting patients, bone marrow samples (2-3 ml) will be collected in heparinized tubes at the following time points: pre-study, and at the end of Cycle 1 on the same day as bone marrow evaluation.

Record the exact time the sample is drawn.

Blood Sample No.	Time Point	Scheduled Collection Time	Actual Date Sample Collected	Actual Time Sample Collected (24-hr clock)
1	**Pre-study**	Pre-study	___/___/__	|__|__| : |__|__|
2	**End of Cycle 1**	Same day as bone marrow evaluation	___/___/__	|__|__| : |__|__|

One copy of this Pharmacodynamic 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 – mRNA Transcript Level samples.

Signature: _____ Date:_____
(site personnel who collected samples)

APPENDIX VIII-A: THERAPY DELIVERY MAP FOR CYCLE 1

Therapy Delivery Map – Cycle 1 This Therapy Delivery Map (TDM) relates to Cycle 1. Each cycle lasts 35 days.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are in Section 5.3. Extensive treatment details are in Section 5.2.
This TDM is on 4 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
IT Cytarabine (ARAC) (all patients)	Intrathecal (IT)	Age-based dosing: **Age (yrs) Dose** < 1 20 mg 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg	0	Given at the time of diagnostic lumbar puncture **OR** Day 0.
IT Cytarabine (CNS 2 or 3 patients)*	IT	Age-based dosing: **Age (yrs) Dose** < 1 20 mg 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg	Twice weekly	A minimum of 4 and a maximum of 6 (count includes day 0 IT) intrathecal treatments may be given. The choice between IT Cytarabine **OR** IT Triples for patients with CNS 2 or 3 is up to the treating physician's discretion.
IT Triples (Methotrexate/ Hydrocortisone /Cytarabine) (CNS 2 or 3 patients)*	IT	Age-based dosing: **Age (yrs) Dose** < 1 MTX: 7.5 mg, HC: 7.5 mg, ARAC: 15 mg 1-1.99 MTX: 8 mg, HC: 8 mg, ARAC: 16 mg 2-2.99 MTX: 10 mg, HC: 10 mg, ARAC: 20 mg 3-8.99 MTX: 12 mg, HC: 12 mg, ARAC: 24 mg ≥ 9 MTX: 15 mg, HC: 15 mg, ARAC: 30 mg	Twice weekly	A minimum of 4 and a maximum of 6 (count includes day 0 IT) intrathecal treatments may be given. The choice between IT Cytarabine **OR** IT Triples for patients with CNS 2 or 3 is up to the treating physician's discretion.
Azacitidine (AZA)	IV over 15 minutes	Age-based dosing: **Age (yrs) Dose** < 1 2.5 mg/kg/dose ≥ 1 75 mg/m^2/dose	1-5	On days 1, 3, and 5, administer before MLN4924 (pevonedistat) infusion. See below for timing.
MLN4924	Intravenous (IV)	**Patients < 1 year of age:**	1, 3, 5	Administer 30-60 minutes after completion

Cycle 1

(Pevonedistat)	over 1 hour	Dose Level -1: 10 mg/m^2 Dose Level 1: 15 mg/m^2 **Patients ≥ 1 year of age:** Dose Level -1: 15 mg/m^2 Dose Level 1: 20 mg/m^2		of azacitidine.
Fludarabine (FLU)	IV over 30 minutes	Age-based dosing: **Age (yrs) Dose** < 1 1 mg/kg/dose ≥ 1 30 mg/m^2/dose	6-10	
Cytarabine (ARAC)	IV over 1-3 hours	Age-based dosing: **Age (yrs) Dose** < 1 67 mg/kg/dose ≥ 1 2000 mg/m^2/dose	6-10	Use eye drops as described in Section 5.2. To begin 4 hours after the start of the fludarabine infusion.

*CNS2 and CNS 3 patients will receive additional IT cytarabine OR IT triples 2x/weekly until the CNS is clear of blasts on 2 consecutive LPs, with a minimum of 4 IT cytarabine OR IT Triples doses administered. Days of therapy may vary depending on scheduling.

Ht _____cm **Wt _____kg** **BSA _____m^2** **Dose Level _____mg/m^2**

Date Due	Date Given	Day	IT* ARAC _____ mg	IT* Triples _____ mg	AZA _____ mg	MLN4924 (Pevonedistat) _____ mg	FLU _____ mg	ARAC _____ mg	Studies	
			Enter calculated dose above and actual dose administered below							
		Pre-	_____ mg						a – m, p	
		1			_____ mg	_____ mg			e, n, o, p, q	
		2			_____ mg					a,
		3			_____ mg	_____ mg			e, n, p, q	b,
		4			_____ mg					d,
		5			_____ mg	_____ mg			e, n, p, q	f,
		6					_____ mg	_____ mg		g
		7					_____ mg	_____ mg		

Cycle 1

		8	_____ mg*	_____ mg*			_____ mg	_____ mg		a, b, d, f, g, p
		9					_____ mg	_____ mg		
		10					_____ mg	_____ mg		
		11								
		12								
		13	_____ mg*	_____ mg*						
		14								
		15	_____ mg*	_____ mg*						a, b, d, f, g, p
		16								
		17								
		18								
		19								
		20	_____ mg*	_____ mg*						
		21								
		22	_____ mg*	_____ mg*						a, b, d, f, g, p
		23								
		24								
		25								
		26								
		27								
		28								
		29								a, b, d, f, g, p
		30								
		31								
		32								
		33								
		34								
		35							l, m, o	

*CNS2 and CNS 3 patients will receive additional IT cytarabine OR IT triples 2x/weekly until the CNS is clear of blasts on 2 consecutive LPs, with a minimum of 4 IT cytarabine OR IT triples doses administered. Days of therapy may vary depending on scheduling.

Cycle 1

Required Observations in Cycle 1

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Hx/Wt /Ht/BSA. Prior to Cycle 1 and every week during Cycle 1.
b. Physical exam (including VS). Prior to Cycle 1 and every week during Cycle 1.
c. Performance Status. Prior to Cycle 1.
d. CBC/diff/platelets. Prior to Cycle 1 and twice weekly during Cycle 1.
e. Pharmacokinetics. In patients ≤ 10 kg, samples to be collected on Day 1 and Day 5 pre-MLN4924 (pevonedistat) dose, at the end of MLN4924 (pevonedistat) infusion, and at 4 – 6 hours, and 24 hours after the end of MLN4924 (pevonedistat) infusion. In patients > 10 kg, samples to be collected on Day 1 pre-MLN4924 (pevonedistat) dose, at the end of MLN4924 (pevonedistat) infusion, and at 1, 2, 4, 6 – 8, and 24 hours after the end of MLN4924 (pevonedistat) infusion; on Day 3 pre-MLN4924 (pevonedistat); and on Day 5 pre-MLN4924 (pevonedistat) dose, at the end of MLN4924 (pevonedistat) infusion, and at 1, 2, 4, 6 – 8, 24, and 48 **OR** 72 hours after the end of MLN4924 (pevonedistat) infusion. See Section 8.2 for details.
f. Electrolytes including Ca^{++}, Mg^{++}, PO_4. Prior to Cycle 1 and weekly during Cycle 1.
g. Creatinine. Prior to Cycle 1 and weekly during Cycle 1.
h. Albumin. Prior to Cycle 1.
i. Pregnancy test. Prior to Cycle 1.
j. ECHO or gated radionuclide study. Prior to Cycle 1.
k. EKG. Prior to Cycle 1.
l. Bone marrow aspirate and/or biopsy. Prior to Cycle 1 and at the end of Cycle 1.
m. CSF for cell count, cytospin. Prior to Cycle 1 and at the end of Cycle 1.
n. Pharmacodynamics (mRNA Transcript Levels). Optional samples to be collected on day 1 pre-MLN4924 (pevonedistat) dose and on day 3 **OR** day 5 at 3 hours and 6 hours after the end of MLN4924 (pevonedistat) infusion. See Section 8.3 for details.
o. Pharmacodynamics (NEDDylated Protein Analysis). Optional samples to be collected on day 1 pre-MLN4924 (pevonedistat) dose, and at 10 hours and 24 hours after the end of MLN4924 (pevonedistat) infusion. An additional sample is to be collected at the end of Cycle 1 on the same day as bone marrow evaluation. See Section 8.4 for details.
p. ALT, AST, Bilirubin. Prior to Cycle 1, prior to each dose of MLN4924 (pevonedistat), and then weekly.

q. Vital signs. Prior to each dose of MLN4924 (pevonedistat).

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)

Cycle 1

APPENDIX VIII-B: THERAPY DELIVERY MAP FOR CYCLE 2

Therapy Delivery Map – Cycle 2 This Therapy Delivery Map (TDM) relates to Cycle 2. Each cycle lasts 35 days.	_____ Patient COG ID number _____ DOB

Criteria to start each cycle are listed in Section 5.3. Extensive treatment details are in Section 5.2.
This TDM is on 3 pages.

DRUG	ROUTE	DOSAGE	DAYS	IMPORTANT NOTES
IT Cytarabine (ARAC) (all patients)	Intrathecal (IT)	Age-based dosing: **Age (yrs) Dose** < 1 20 mg 1-1.99 30 mg 2-2.99 50 mg ≥ 3 70 mg	0	Given at the time of bone marrow aspirate/biopsy at the end of Cycle 1 **OR** on Day 0 of Cycle 2. See Section 5.2 and Section 5.3 for full details.
Azacitidine (AZA)	IV over 15 minutes	Age-based dosing: **Age (yrs) Dose** < 1 2.5 mg/kg/dose ≥ 1 75 mg/m^2/dose	1-5	On days 1, 3, and 5, administer before MLN4924 (pevonedistat) infusion. See timing below.
MLN4924 (Pevonedistat)	Intravenous (IV) over 1 hour	**Patients < 1 year of age:** Dose Level -1: 10 mg/m^2 Dose Level 1: 15 mg/m^2 **Patients ≥ 1 year of age:** Dose Level -1: 15 mg/m^2 Dose Level 1: 20 mg/m^2	1, 3, 5	Administer 30-60 minutes after completion of azacitidine.
Fludarabine (FLU)	IV over 30 minutes	Age-based dosing: **Age (yrs) Dose** < 1 1 mg/kg/dose ≥ 1 30 mg/m^2/dose	6-10	
Cytarabine	IV over 1-3	Age-based dosing:	6-10	Use eye drops as described in Section 5.2.

Cycle 2

(ARAC)	hours	**Age (yrs)** **Dose** < 1 67 mg/kg/dose ≥ 1 2000 mg/m^2/dose		To begin 4 hours after the start of the fludarabine infusion.

Ht _____cm **Wt _____kg** **BSA _____m^2** **Dose Level _____mg/m^2**

Date Due	Date Given	Day	IT ARAC _____ mg	AZA _____ mg	MLN4924 (Pevonedistat) _____ mg	FLU _____ mg	ARAC _____ mg	Studies	
			Enter calculated dose above and actual dose administered below						
		Pre-	_____ mg					a – f , h, i, k	
		1		_____ mg	_____ mg			g, l	
		2		_____ mg					
		3		_____ mg	_____ mg			g, l	
		4		_____ mg					
		5		_____ mg	_____ mg			g, l	
		6				_____ mg	_____ mg		
		7				_____ mg	_____ mg		
		8				_____ mg	_____ mg		
		9				_____ mg	_____ mg		
		10				_____ mg	_____ mg		
		11							g
		12							
		13							
		14							
		15							
		16							
		17							
		18							g
		19							
		20							
		21							
		22							g

Cycle 2

		23							
		24							
		25							
		26							
		27							
		28							
		29							
		30							
		31							
		32							g
		33							
		34							
		35						h – k	

Required Observations in Cycle 2

a. Hx/Wt /Ht/BSA. Prior to Cycle 2.
b. Physical exam (including VS). Prior to Cycle 2.
c. CBC/diff/platelets. Prior to Cycle 2.
d. Electrolytes including Ca^{++}, Mg^{++}, PO_4. Prior to Cycle 2.
e. Creatinine. Prior to Cycle 2.
f. Albumin. Prior to Cycle 2.
g. ALT, AST, Bilirubin. Prior to each dose of MLN4924 (pevonedistat), then weekly.
h. ECHO or gated radionuclide study. Prior to Cycle 2 and at the end of Cycle 2.
i. EKG. Prior to Cycle 2 and at the end of Cycle 2.
j. Bone marrow aspirate and/or biopsy. At the end of Cycle 2.
k. CSF for cell count, cytospin. With day 0 IT and at the end of Cycle 2.
l. Vital signs. Prior to each dose of MLN4924 (pevonedistat).

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)

Cycle 2

APPENDIX IX: 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
acalabrutinib[5] alfentanil[4,5] 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] eplerenone[5] ergotamine[4] 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] tamoxifen telaprevir 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 7.4.1 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 X: PATIENT DRUG INTERACTIONS HANDOUT AND WALLET CARD

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

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

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

These are the things that your healthcare providers need to know:
MLN4924 (pevonedistat) interacts with certain specific enzyme in your liver or other tissue like the gut and certain transport proteins that help move drugs in and out of cell.

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

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

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

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

Version JAN/2019

PATIENT DRUG INTERACTION WALLET CARD

NIH NATIONAL CANCER INSTITUTE

EMERGENCY INFORMATION

Show this card to all of your healthcare providers. Keep it with you in case you go to the emergency room.

Patient Name:

Diagnosis:

Study Doctor:

Study Doctor Phone #:

NCI Trial #:

Study Drug(S): MLN4924 (pevonedistat)

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

NIH NATIONAL CANCER INSTITUTE

Tell your doctors **before** you **start** or **stop** any medicines.

Check with your doctor or pharmacist if you need to use an over-the-counter medicine or herbal supplement!

Use caution and avoid the following drugs if possible:

St. John's Wort, grapefruit or grapefruit juice

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

NIH NATIONAL CANCER INSTITUTE

DRUG INTERACTIONS

Carry this card with you at all times

MLN4924 (pevonedistat) interacts with enzymes in your liver or other tissue like the gut, transport proteins that help move drugs in and out of cells and must be used very carefully with other medicines.

Your healthcare providers should be aware of any medicines that are strong inhibitors/inducers of CYP3A4/5, P-gp and OATP. Drugs that are CYP3A4/5 inducers (e.g., rifampin, St. John's Wort), or BCRP inhibitors (e.g., cyclosporine) ae not allowed.

Before prescribing new medicines, your health care provider should check a **frequently-updated medical reference** for a **list of drugs to avoid** or contact your study doctor.

Version JAN/2019

For more information: 1-800-4-CANCER
cancer.gov | clinicaltrials.gov

APPENDIX XI: NEW YORK HEART ASSOCIATION CLASSIFICATION OF CARDIAC DISEASE

The following table presents the New York Heart Association classification of cardiac disease.[33]

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 XII: CTEP AND CTSU REGISTRATION PROCEDURES

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

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

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

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

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

CTSU Registration Procedures

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

IRB Approval:
Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

Requirements For ADVL1712 Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted)
- For applicable studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

Submitting Regulatory Documents:
Submit required forms and documents to the CTSU Regulatory Office, 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.

APPENIX XIII: GUIDELINES FOR SHIPPING SAMPLES TO COVANCE – MADISON

Packing Instructions

1. Place samples into a divided specimen box in the exact order of the pharmacokinetic study form (Appendix IV-A and/or Appendix IV-B).
2. Place enough absorbent material to absorb at least three times the contents.
3. Secure the lid on the specimen box and seal the box inside a biohazard sample transport bag.
4. Place the specimen boxes in the center of an insulated shipping container.
5. Surround and cover the contents with at least enough dry ice to last the duration of the journey.
    - Dry ice recommendations:
        - Large Styrofoam cooler, between 12 to 14 kg of pellet dry ice.
        - Medium Styrofoam cooler, between 10 to 12 kg of pellet dry ice.
        - Small Styrofoam cooler, between 7 to 10 kg of pellet dry ice (amount dependent on actual box size).

    Note: Block dry ice or ice packs should never be used to ship bioanalytical samples.
6. Include a hard copy of the pharmacokinetic study form (Appendix IV-A and/or Appendix IV-B) in a water proof bag.
7. Add packing material to prevent contents from shifting during transport and secure the lid.
8. Place the shipping container in a shipping box and securely close the box. Use tape that is resistant to moisture and cold.
9. Place Biohazard warnings on outside of box (if applicable).
10. Label the box exterior in accordance with the applicable DOT CFR / IATA Regulations.

Shipping Instructions

Unless otherwise directed, address the shipment to:

Attention: Melanie Ivancic, PhD
Sample Management—Bioanalytical (Rm 1S 160)
Covance Laboratory Inc.
3301 Kinsman Boulevard
Madison, WI 53704-2523

The pharmacokinetic study form should be attached to an e-mail sent to both the study-specific Research Coordinator as well as Madison.SA@covance.com on the day of shipping as notification of the intended shipment.

When possible, shipments should be made Monday through Wednesday. Specify a Priority A.M. delivery to Covance. Sample shipments should be made at least 2 days prior to a United States National Holiday. For shipments that may result in a weekend or holiday delivery, please contact the Bioanalytical Principal Investigator and Madison.SA@covance.com to discuss delivery details.

Any questions regarding shipping instructions may be directed to phone number (608) 395-3750 or via email at SampleInformationCoordination@covance.com.

Regulatory Information

Specific Federal and International Regulations define classes of "Hazardous Materials"[1] and "Dangerous Goods"[2]. Specimens transported to the Covance- 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 49[3] 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.

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