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


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


January 31, 2019

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Dear Ms. Kruhm,

Enclosed please find Amendment #4 to **ADVL1513**, *A Phase 1 Study of Entinostat, an Oral Histone Deacetylase Inhibitor, in Pediatric Patients with Recurrent or Refractory Solid Tumors, Including CNS Tumors and Lymphoma*.

The protocol has been amended in response to the Request for Amendment from Dr. Malcolm Smith, dated December 20, 2018, in which COGC transitions to PEP-CTN.

Please contact us if you have any further questions.

Sincerely,

Alina Stout, Protocol Coordinator for
Andrew Bukowinski, M.D., **ADVL1513** Study Chair, and
Brenda Weigel, M.D., PI, PEP-CTN

## I. Protocol Changes:

| # | Section | Comments |
|---|---|---|
| 1. | Title Page | The version date has been updated.<br><br>The amendment number has been updated.<br><br>The "Lead Organization" has been updated.<br><br>The list of "Participating Organizations" has been removed.<br><br>The following sentence has been revised:<br><br>"For ~~COG Phase 1 Pilot Consortium Operations~~**PEP-CTN Operations and Data/Statistics** Contacts see: http://members.childrensoncologygroup.org" |
| 2. | TOC | The Table of Contents has been updated. |
| 3. | Study Committee | The following sentence has been revised:<br><br>"For ~~COG Phase 1/Pilot Consortium Contacts~~**PEP-CTN Operations and Data/Statistics Contacts** see: …" |
| 4. | Certificate of Confidentiality | The following sentence has been revised:<br><br>"~~The Children's Oncology Group has received~~**his trial is covered by** a Certificate of Confidentiality…" |
| 5. | 13.3 | The CTEP-AERS sponsor email address has been updated from "~~COGCADEERS@childrensoncologygroup.org~~" to "**PEPCTNAERS@childrensoncologygroup.org**". |
| 6. | 14.4 | References to "Developmental Therapeutics" have been replaced with references to "PEP-CTN". |

## II. Informed Consent Document Changes:

| # | Section | Comments |
|---|---|---|
| 7. | General | The version date has been updated. |
| 8. | 1st page | References to the "Phase 1 Consortium" have been replaced with references to PEP-CTN. |
| 9. | "Will my medical information …?" | The following sentence has been revised:<br><br>"T~~he Children's Oncology Group has received~~**his trial is covered by** a Certificate of Confidentiality…" |

Activated: December 27, 2016
Closed:

Version Date: 01/31/19
Amendment # 4

# CHILDREN'S ONCOLOGY GROUP

## ADVL1513

## A PHASE 1 STUDY OF ENTINOSTAT, AN ORAL HISTONE DEACETYLASE INHIBITOR, IN PEDIATRIC PATIENTS WITH RECURRENT OR REFRACTORY SOLID TUMORS, INCLUDING CNS TUMORS AND LYMPHOMA

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



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

# TABLE OF CONTENTS

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**AGENT NSC# AND IND#'s**

NCI-Supplied Agent:
Entinostat (SNDX-275, MS-275, NSC#706995, [redacted]

**IND Sponsor:** CTEP

**SEE SECTION 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.

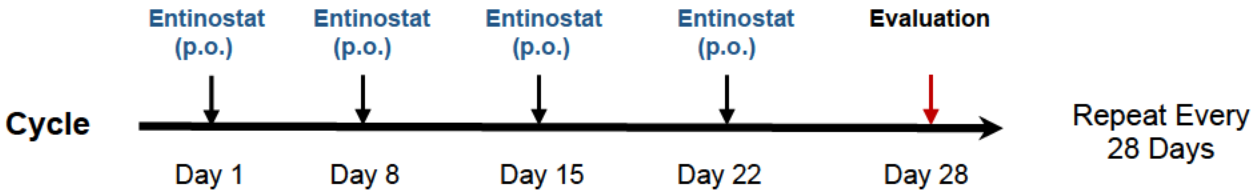
The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

## ABSTRACT

Entinostat is a novel, oral small molecule inhibitor of class I histone deactylases (HDAC). Histone modification plays a key role in oncogenesis and progression of malignancy; HDAC inhibition has the potential to reactive expression of repressed tumor suppressor genes and reverse oncologic processes, leading to cell cycle arrest and differentiation of cancer cells. Entinostat has *in vitro* growth inhibitory activity against a variety of human cancer cell lines, and has shown clinical activity in early phase trials in adults with estrogen-receptor positive breast cancer, Hodgkin lymphoma, and melanoma. Entinostat has also demonstrated potent anti-tumor activity against a variety of pediatric cancer cells lines, including rhabdomyosarcoma, neuroblastoma, Ewing sarcoma, retinoblastoma, osteosarcoma, and medulloblastoma.

We are conducting a pediatric phase 1 trial of single-agent oral entinostat given on a once weekly schedule in children with refractory or recurrent solid tumors, including CNS tumors and lymphoma. The study will use the rolling six design with the primary aim of determining the maximum-tolerated pediatric dose of entinostat. The study will also assess the toxicity profile and determine the pharmacokinetics of entinostat in children with solid tumors.

## EXPERIMENTAL DESIGN SCHEMA




Once weekly treatment with entinostat will be discontinued if there is evidence of progressive disease or drug-related dose-limiting toxicity that requires removal from therapy. Patients with stable disease or greater response may

continue receiving protocol therapy provided that the patient meets the criteria for starting subsequent cycles (Section 5.2) and does not meet any of the criteria for removal from protocol therapy or off study criteria (Section 10.0).

# 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

## 1.1 Primary Aims

1.1.1 To estimate the maximum tolerated dose (MTD) and/or recommended Phase 2 dose of entinostat administered as a single-agent, once weekly to children with recurrent or refractory solid tumors.

1.1.2 To define and describe the toxicities of entinostat administered as a single agent, once weekly to children with recurrent or refractory solid tumors.

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

## 1.2 Secondary Aims

1.2.1 To preliminarily define the antitumor activity of entinostat within the confines of a Phase 1 study.

1.2.2 To assess change in histone H3 and H4 acetylation in peripheral blood mononuclear cells (PBMCs) as a marker of the biologic activity of entinostat.

# 2.0 BACKGROUND

## 2.1 Introduction/Rationale for Development

HDAC inhibitors as anti-cancer agents

Epigenetic processes provide a mechanism for controlling gene expression by impacting chromatin configuration. Along with methylation, acetylation of histones plays a key role in regulating gene expression by controlling the interaction between histones and DNA.[1] Histone acetylation relaxes the chromatin conformation and allows access of transcription factors to DNA promoter regions, thus leading to gene expression. Histone acetyl transferases (HAT) and histone deacetylase (HDAC) enzymes modulate acetylation, which determines whether the nucleosome complex is in a more compact or open state.[2]

Processes that control cell fate, such as cell cycle progression, differentiation, and apoptosis are strongly influenced by acetylation status of histones and the resultant impact on gene transcription. There are four classes of HDACs, which are grouped by their homology to yeast proteins.[3] The Class I family consists of HDACs 1, 2, 3, and 8. The Class II family contains HDACs 4, 5, 7, and 9 (class IIa) as well as HDACs 6 and 10 (class IIb). Class III HDACs are also known as SIRTs and include seven family members. The class IV family

only includes HDAC 11. The relative role of each of the HDACs in biologic processes continue to be elucidated.

Considerable evidence now implicates histone modification in oncogenesis. HDACs play an important role in cell differentiation and also modulate the balance between pro- and anti-apoptotic processes in cells. Deacetylation by HDACs alters the activity of many transcription factors that play a role in cancer, including c-Myc, E2F, p53, and nuclear factor kB.[2] Dysregulation of histone acetylation may lead to aberrant repression of tumor suppressor genes, resulting in maintenance of malignant phenotype. Many cancer cells show high levels of HDAC expression and hypoacetylation of histones.[4]

HDAC inhibition is thought to reactivate abnormally repressed expression of pro-apoptotic genes in tumor cells. HDAC inhibitors lead to cell cycle arrest and differentiation in many cancer cell lines. Several HDAC inhibitors are in various stages of development.

Entinostat (SNDX-275)

Entinostat (SNDX-275) is an oral small molecule inhibitor of class I and IV HDACs (HDACs 1, 2, 3, and 11).[3] Entinostat has demonstrated significant growth inhibitory activity against cancer cells *in vitro*.[5,6] Entinostat has also shown *in vivo* anti-tumor activity in a variety xenograft models.[3,7] The potency and selectivity for specific HDAC isoforms may separate entinostat from other HDAC inhibitors in clinical development. In contrast to other HDAC inhibitors in clinical development, entinostat inhibits class I HDACs more potently than class II HDACs. As there is some *in vitro* data that inhibition of class I HDACs is sufficient to induce apoptosis in cancer cell lines, entinostat may demonstrate anti-tumor activity with limited clinical toxicity against a variety of cancers.[7]

Entinostat strongly inhibits the class I HDACs, HDACs 1, 2, and 3 with $IC_{50}$ values of 0.119 μM, 0.123 μM, and 0.181 μM, respectively.[8] The agent also inhibits HDAC 11 with an $IC_{50}$ of 0.427 μM, but is considerably less effective at inhibiting other HDACs. Growth of several human cancer cell lines was inhibited by entinostat with $IC_{50}$ values ranging from 0.041 to 4.71 μM. Entinostat was most potent against ovarian cancer ($IC_{50}$ = 0.0415 μM), lung cancer ($IC_{50}$ = 0.0195 μM), leukemia ($IC_{50}$ = 0.0212-0.589 μM), and gastric cancer ($IC_{50}$ = 0.820 μM) cell lines.[7] Along with *in vitro* cell growth inhibition, increased levels of the cell cycle inhibitor p21 and cell cycle arrest were observed. In addition, hyperacetylation of histones was seen in tumor cell lines at concentrations of 0.3 μM and 1 μM. Entinostat also demonstrated significant *in vivo* antitumor activity against xenograft models of melanoma, prostate, breast, and non-small cell lung cancer.[9]

Rationale for use of HDAC inhibitors in combination with other anti-cancer agents includes, the increased expression of pro-apoptotic genes with these agents. Many HDAC inhibitors have been tested in combination with cytotoxic chemotherapy and radiation therapy. In estrogen receptor positive breast cancer models, combination of entinostat overcomes resistance to aromatase inhibitors.[10] Entinostat also shows synergy with EGFR inhibition in lung cancer cell lines.[11]

## 2.2 Preclinical Studies

### 2.2.1 Antitumor Activity

Pediatric solid tumors commonly exhibit alterations in transcription factors whose target genes regulate cell proliferation, differentiation, and survival. HDAC inhibitors have the potential to allow expression of genes repressed through epigenetic mechanisms. For this reason, HDAC inhibitors have been tested *in vitro* against a variety of pediatric cancer cell lines. Cell lines from neuroblastoma, Ewing sarcoma, retinoblastoma, osteosarcoma, and medulloblastoma were inhibited at entinostat sub-micromolar concentrations.[6] Entinostat demonstrated more potent *in vitro* inhibition than vorinostat against several pediatric solid tumor cell lines, including the Rh30 rhabdomyosarcoma cell line (entinostat $IC_{50}$ = 0.062 μM versus vorinostat $IC_{50}$: 1.72 μM) and TC-71 Ewing sarcoma cell line (entinostat $IC_{50}$ = 0.10 μM versus vorinostat $IC_{50}$ = 1.28 μM).[6,12] Similar to the HDAC inhibitors vorinostat and sodium butyrate, treatment of Ewing sarcoma cells with entinostat leads to histone acetylation, growth inhibition, and apoptosis.[13]

In cell lines derived from osteosarcoma lung metastases, entinostat induces Fas ligand mediated cell death through downregulation of the apoptosis inhibitor, c-FLIP. *In vivo* treatment with entinostat resulted in decreased c-FLIP expression and induced tumor regression in nu/nu-mice with osteosarcoma lung metastases.[14] Growth of established tumors in neuroblastoma and Ewing sarcoma models were also significantly suppressed with entinostat doses of 24.5 mg/kg given every 5-7 days.[6]

In alveolar rhabdomyosarcoma, *Pax3:Foxo1* fusion oncogene mediates resistance to cytotoxic chemotherapy and radiation. There is some evidence that *Pax3:Foxo1* expression may be epigenetically regulated. Treatment with entinostat silences protein and mRNA expression of *Pax3:Foxo1* in both mouse and human alveolar rhabdomyosarcoma (ARMS) cells.[15] In contrast, treatment with vorinostat appears to have no effect on *Pax3:Foxo1* expression in human ARMS cells. Moreover, through apparent downregulation of *Pax3:Foxo1* expression, entinostat separately shows synergy with each vincristine, actinomycin-D, and radiation therapy in an orthotopic mouse model of alveolar rhabdomyosarcoma. Entinostat appears to enhance the effects of vincristine in embryonal rhabdomyosarcoma as well, although the mechanism for this effect is unclear.[16]

Data suggests that aberrant regulation of histone acetylation also plays in the progression and maintenance of pediatric central nervous system (CNS) tumors. As a single-agent, vorinostat has shown activity against glioma, medulloblastoma, and supratentorial primitive neuroectodermal tumor cells.[17-19] Several studies have shown synergy with vorinostat and radiation in pediatric brain tumor cells.[20] The Children's Oncology Group ACNS0927 study evaluated vorinostat in combination with radiation therapy for children with diffuse intrinsic pontine glioma, and efficacy data from this study is pending. Similar to vorinostat, entinostat enhances the effect of radiation in human glioma cells.[21] In addition, entinostat enhances chemotherapy-induced apoptosis in primary human medulloblastoma cells by

promoting p53-dependent activation of Bax.[22] In combination with doxorubicin and other chemotherapeutic agents, entinostat induces apoptosis in glioblastoma cells and suppresses growth of medulloblastoma tumors *in vivo*.[22,23]

HDAC inhibitors and entinostat, in particular, may also be relevant in hematologic malignancies. In Hodgkin lymphoma cell lines, entinostat inhibits proliferation and induces cell death. The anti-cancer activity of entinostat correlates with increased H3 acetylation and upregulation of p21 expression.[24]

#### 2.2.2 Animal Toxicology

Single-dose toxicology studies were conducted in mice and rats. Maximum non-lethal doses were 380 mg/kg in mice and 150 mg/kg in rats. Repeated doses administered to rats, beagle dogs, and cynomolgus monkeys demonstrated toxic effects on tissues with high cellular turnover. Adverse effects included fur thinning, scabbing of skin, atrophy of lymphatic organs, and bone marrow toxicity (leukopenia, anemia, and thrombocytopenia). Gastrointestinal toxicity was noted in monkeys (diarrhea, vomiting) and rats (diarrhea, reduced food consumption). Toxic effects on reproductive organs and fertility were noted, and embryo-fetal toxicity was noted in rats and rabbits at doses below 2 mg/kg daily.

#### 2.2.3 Preclinical Pharmacokinetic Studies

Preclinical pharmacokinetics of entinostat have been evaluated in mice, rats, dogs, and monkeys using a liquid chromatography-mass spectroscopy method to measure concentrations. Peak plasma concentrations were achieved between 5 and 30 minutes after oral administration to mice, rats, and dogs and 2 hours after dosing in monkeys. Oral bioavailability after a single dose ranged from 30% in dogs to 80% in monkeys. In dogs, lower gastric pH increased absorption of entinostat from 30% to 55%, and feeding decreased absorption compared to fasting.

Entinostat was moderately metabolically stable in liver microsomes of humans and all animal species evaluated as well as in human cytochrome P-450 preparations. Reversible inhibition by entinostat was noted for CYP2C8 and CYP3A4. Moderate reversible inhibition was also demonstrated for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, and CYP2E1, but only by > 50% at the highest concentrations. Entinostat did not inhibit any UGT enzymes. It was found to induce CYP1A2, CYP2C6, and CYP2B8 as well as UGT1A4. No formal drug interaction studies have been performed.

Entinostat was excreted to a similar extent in urine and feces of albino and pigmented rats, with 68% to 85% excreted in the first 24 hours.

### 2.3 **Adult Studies**

#### 2.3.1 Phase 1 Studies

Several clinical studies of entinostat have been completed in adults. Six trials (NCI or industry-sponsored) using entinostat as monotherapy have been completed. In a phase 1 study in adults with refractory solid tumors and lymphoma, daily oral administration was not tolerable as the first two patients experienced DLT at the first dose level of 2 mg/m$^2$.[25]

Pharmacokinetic analysis showed the half-life to be 39 to 80 hours. Twenty-eight patients were treated on a once every 14-day schedule. The MTD was 10 mg/m$^2$ and dose-limiting toxicities were grade 3 fatigue, anorexia, nausea, and vomiting.

In another phase 1 trial in adults with refractory solid tumors and lymphoid malignancies, entinostat was administered orally once weekly for 4 weeks of a 6-week cycle.[26] Among 19 evaluable patients, no grade 4 toxicities were observed. DLTs were grade 3 hypophosphatemia, hyponatremia, and hypoalbuminemia. The MTD was 6 mg/m$^2$ on this schedule. An additional phase 1 trial or entinostat evaluated multiple schedules.[27] Toxicities were similar to other phase 1 trials and DLTs were hypophosphatemia and asthenia. A twice-weekly schedule was found to not be tolerable, and the recommended phase 2 dose (RP2D) was 4 mg/m$^2$ when entinostat is given weekly for 3 weeks every 28 days.

Several adult phase 1 combination trials with entinostat and other agents (including azacytidine, 13-cis-retinoic acid, imatinib, sorafenib, clofarabine, and lapatanib) have been completed or are ongoing.

### 2.3.2 Phase 2 Studies

Two phase 2 single-agent trials of entinostat in adults have been completed. Single-agent entinostat (15 mg weekly or 10-15mg every other week) was well tolerated and demonstrated tumor reduction in 63% of evaluable patients in a phase 2 trial for patients with refractory Hodgkin's lymphoma.[28] A phase 2 study using 2 different dosing scheduled of single-agent entinostat for patients with metastatic melanoma showed no objective responses, but stable disease in 25% of patients.[29] Several phase 2 combination studies for adult patients with non-small cell lung cancer, breast cancer, hematologic malignancies, colorectal cancer, and renal cell carcinoma are ongoing or have been completed. Entinostat with exemestane was compared to exemestane plus placebo in a randomized phase 2 trial for patients with recurrent or metastatic estrogen receptor-positive breast cancer.[30] Treatment with the entinostat combination improved PFS to 4.3 months versus 2.3 months (one-sided $p = 0.055$) and improved overall survival from 19.8 months to 28.1 months (one-sided $p = 0.018$). Based on these data, entinostat has received Breakthrough Therapy designation from the U.S. Food and Drug Administration (FDA). The combination of entinostat and exemestane is being evaluated in a Phase 3 trial for postmenopausal women with metastatic ER-positive breast cancer whose disease has progressed on hormonal therapy.

Based on the compiled results of clinical trials thus far, the recommended dose regimens for further development of entinostat in adults are 5 mg once weekly, 10 mg once every 2 weeks, and 7 to 15 mg weekly for 3 weeks of a 4-week cycle.

2.3.3 Pharmacology/Pharmacokinetics/Correlative and Biological Studies

Pharmacokinetics of entinostat were characterized in three separate phase 1 trials.[25,27,31] Variability in pharmacokinetic parameters across the studies was seen, possibly due to different sampling schemes and different assays used in each study. In general, pharmacokinetics for entinostat were linear with proportional AUC and peak concentrations across dose levels up to 12 mg/m$^2$, and toxicity appears to be dose-dependent. Entinostat is not metabolized by CYP enzymes, and the primary elimination pathway is unknown. The elimination half-life of entinostat ranged from 54 to 161 hours in one single-agent Phase 1 study, and ranged from 39 to 80 hours in another study. Pharmacokinetic parameters are not affected by combination treatment with exemestane or erlotinib. Lastly, food appears to impact entinostat PK, and therefore, the agent should be taken on an empty stomach at least 1 hour before and 2 hours after a meal.

In a phase 1 trial, hyperacetylation of histone H3 was seen in peripheral blood mononuclear cells from several patients with solid tumors after administration of entinostat at doses of 2 mg/m$^2$ and 10 mg/m$^2$.[25,27]

## 2.4 Pediatric Studies

2.4.1 Prior Experience in Children

There have been no prior pediatric studies with entinostat.

## 2.5 Overview of Proposed Pediatric Study

This will be a phase 1 dose-escalation trial of entinostat in pediatric patients with recurrent or refractory solid tumors including CNS tumors and lymphoma. The primary study objectives are to identify the maximum tolerated dose (MTD) or recommended phase 2 dose (RP2D), characterize the toxicity profile, evaluate the change in histone acetylation, and describe the pharmacokinetics of entinostat in pediatric patients with solid tumors.

Patients age 1 to 21 years with recurrent or refractory solid tumors, including CNS tumors and lymphoma will be eligible. Entinostat will be administered orally at a starting dose of 3 mg/m$^2$ once weekly, which is equivalent to the RP2D of 5 mg in adults when entinostat is administered on a weekly schedule. Entinostat will be administered continuously once weekly in 28-day cycles. Cohorts will be enrolled and doses escalated using the rolling six design.[32] Doses will be escalated by approximately 30% in each subsequent cohort.

The MTD will be determined from toxicities observed during the first cycle of treatment. The MTD will be the dose level below which ≥ 2 out a cohort of up to 6 patients experience DLTs. Disease evaluations will be performed at the end of Cycle 1, then every other cycle for 2 cycles, then every 3 cycles. Pharmacokinetic and pharmacodynamic sampling will be performed during the 1$^{st}$ cycle of treatment.

# 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 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.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 started must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

3.10 **Dose Assignment**

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

## 4.0 PATIENT ELIGIBILITY

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

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

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

## 4.1 Inclusion Criteria

4.1.1 Age: Patients must be ≥ than 12 months and ≤ 21 years of age at the time of study enrollment.

4.1.2 Patients must have a BSA of ≥ 1.17 $m^2$ at time of study enrollment.

4.1.3 Patients must be able to swallow intact tablets.

4.1.4 Diagnosis: Patients with recurrent or refractory solid tumors, including CNS tumors or lymphoma, are eligible. Patients must have had histologic verification of malignancy at original diagnosis or relapse except in patients with intrinsic brain stem tumors, optic pathway gliomas, or patients with pineal tumors and elevations of CSF or serum tumor markers including alpha-fetoprotein or beta-HCG.

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

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

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

4.1.8 Prior Therapy
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 defined 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.

*i.* *Solid Tumor Patients*: ≥ 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).

*ii.* *Lymphoma Patients*:

- A waiting period prior to enrollment is not required for patients receiving standard cytotoxic maintenance chemotherapy (i.e. corticosteroid, vincristine, 6MP, and/or methotrexate).

- ≥ 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 fully 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 must have elapsed from 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 must have elapsed from 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 must have elapsed from the last dose 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 must have elapsed from infusion and no evidence of GVHD.

- Autologous stem cell infusion including boost infusion: ≥ 42 days must have elapsed from infusion.

g. Cellular Therapy: ≥ 42 days must have elapsed from last dose 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 must have elapsed after local XRT; ≥ 150 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 must have elapsed from the last dose of systemically administered radiopharmaceutical therapy.

j. HDAC Inhibitors: Patients must not have received prior therapy with entinostat. Patients who have received therapy with other HDAC inhibitors are eligible.

### 4.1.9 Organ Function Requirements

#### 4.1.9.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors, including lymphoma, without known bone marrow involvement:
- Peripheral absolute neutrophil count (ANC) ≥ 1000/mm$^3$
- Platelet count ≥ 100,000/mm$^3$ (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)
- Hemoglobin ≥ 8.0 g/dl, with or without transfusion

b. Patients with known bone marrow metastatic disease will not be eligible.

#### 4.1.9.2 Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70ml/min/1.73 m$^2$ or
- A serum creatinine based on age/gender as follows:

| **Age** | **Maximum Serum Creatinine (mg/dL)** | |
|---|---|---|
| | **Male** | **Female** |
| 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[33] utilizing child length and stature data published by the CDC.

4.1.9.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 3 × ULN = 135 U/l. For the purpose of this study, the ULN for SGPT is 45 U/l.
- Serum albumin ≥ 2 g/dl.

4.1.10 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 studies. 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 an effective contraceptive method both during and for 3 months after participation in this study. Abstinence is an acceptable method of contraception. Those who become pregnant while on treatment with entinostat must discontinue immediately and consult their treating physician.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids:

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

4.2.2.2 Investigational Drugs:

Patients who are currently receiving another investigational drug are not

eligible.

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

4.2.2.4 Patients requiring concurrent administration of valproic acid are not eligible for this trial.

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

4.2.3 Study Specific:

- Patients with a BSA < 1.17 $m^2$ at time of study enrollment are not eligible.
- Patients who are not able to swallow intact tablets are not eligible.

4.2.4 Cardiac:
Patients with a known history of QTc prolongation (> 480 msec), or known history of ventricular tachycardia, ventricular fibrillation or Torsades de pointes are not eligible.

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

4.2.6 Transplantation:
Patients who have received a prior solid organ transplantation are not eligible.

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

4.2.8 Patients with a history of allergy to medications that have a benzamide structure (e.g., metoclopramide, procarbazine, domperidone, cisapride etc.) are not eligible.

# 5.0 TREATMENT PROGRAM

## 5.1 Overview of Treatment Plan

| | | Entinostat oral | Action |
|---|---|---|---|
| Week 1 | Day 1 | X | |
| Week 2 | Day 8 | X | |
| Week 3 | Day 15 | X | |
| Week 4 | Day 22 | X | |
| End of Cycle | Day 28 | | Evaluation |

Entinostat will be administered orally on Days 1, 8, 15, and 22 of a 28-day cycle. Patients may continue to receive entinostat for up to 5 years.

Drug doses should be adjusted based on the BSA calculated from height and weight measured within 7 days prior to the beginning of each cycle. If a patient vomits within 30 minutes after the dose of entinostat is administered, that dose may be repeated. If vomiting occurs greater than 30 minutes after the administered dose, the dose will not be repeated. If a patient misses an entinostat dose and less than 12 hours have passed since the scheduled dosing time, that dose should be taken immediately. If a patient misses an entinostat dose and more than 12 hours have passed since the scheduled dosing time, this dose will be skipped. If a patient accidentally takes an extra dose during a day, the next scheduled dose of entinostat will be skipped.

The patient/family will be asked to complete a Patient Medication Diary (see Appendix V).

## 5.2 Criteria for Starting Subsequent Cycles

A cycle may be repeated every 28 days if the patient has at least stable disease and has again met laboratory parameters as defined in the eligibility section, Section 4.0.Section4_0

## 5.3 Dose Escalation Schema

### 5.3.1 Inter-Patient Escalation

The starting dose will be 3 mg/m$^2$ (dose level 1) with dose levels for subsequent groups of patients as follows.

| Dose Level | Entinostat (mg/m$^2$) | Day(s) of Administration |
|---|---|---|
| - 1 | 2.3 | 1, 8, 15, 22 |
| **1*** | **3** | **1, 8, 15, 22** |
| 2 | 4 | 1, 8, 15, 22 |

*Starting dose level of ~ adult RP2D

There will be no escalations beyond dose level 2 (4 mg/m$^2$), as previous pediatric Phase 1 studies have rarely defined a MTD greater than 160% of the adult MTD.

If the MTD has been exceeded at the first dose level, then the subsequent cohort of patients will be treated at a dose of 2.3 mg/m$^2$ (dose level -1). If dose level -1 is not well tolerated, further de-escalation will not occur. The study will be closed to accrual.

Entinostat doses will be rounded to the nearest 1 mg (see dosing tables in Appendix IV).

5.3.2 Intra-Patient Escalation

Intra-patient dose escalation is not allowed.

## 5.4 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.

## 5.5 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-escalation will be the first cycle of therapy.

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

5.5.1 Non-Hematological Dose-Limiting Toxicity

5.5.1.1 Any Grade 3 or greater non-hematological toxicity attributable to the investigational drug with the specific exclusion of:

- Grade 3 nausea and vomiting of less < 3 days duration
- Grade 3 liver enzyme elevation, including ALT/AST/GGT that returns to levels that meet initial eligibility criteria or baseline within 7 days. See Appendix III for values that represent thresholds between CTCAE grades. Note: For the purposes of this study the ULN for ALT is defined as 45 U/L.
- Grade 3 or 4 fever < 5 days duration.
- Grade 3 infection < 5 days duration.
- Grade 3 hypophosphatemia, hypokalemia, hypocalcemia or hypomagnesemia responsive to supplementation.

- Any Grade 2 non-hematological toxicity that persists for ≥ 7 days and is considered sufficiently medically significant or sufficiently intolerable by patients that it requires treatment interruption.
- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.5.2 Hematological dose limiting toxicity

5.5.2.1 Hematological dose limiting toxicity is defined as:

- Grade 4 thrombocytopenia (platelet count < 25,000/mm$^3$) or Grade 4 neutropenia (see Section 6.1), not due to malignant infiltration.
- Grade 3 thrombocytopenia with clinically significant bleeding, petechiae, or purpura or that persists for ≥ 7 days or that requires platelet transfusion on ≥ 2 separate days within a 7-day period.

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

## 6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

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

### 6.1 Dose Modifications for Hematological Toxicity

6.1.1 If a patient experiences Grade 4 neutropenia or thrombocytopenia, the treatment will be held. Counts should be checked every 3-4 days for thrombocytopenia or neutropenia during this time. If the toxicity resolves to meet eligibility parameters within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level. For patients enrolled at Dose Level -1 (see Section 5.3.1), the dose should be reduced to 1.6 mg/m$^2$. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.1.2 If toxicity does not resolve to meet eligibility parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.1.3 If hematological dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose, the patient must be removed from protocol therapy.

### 6.2 Dose Modifications for Non-Hematological Toxicity

6.2.1 If a patient experiences non-hematological dose-limiting toxicity as defined in Section 5.5.1, the treatment will be held. When the toxicity resolves to meet eligibility parameters or baseline within 14 days of drug discontinuation, the patient may resume treatment at the next lower dose level. For patients enrolled at Dose Level -1 (see Section 5.3.1), the dose should be reduced to 1.6 mg/m$^2$. Doses reduced for toxicity will not be re-escalated, even if there is minimal or no toxicity with the reduced dose.

6.2.2 If toxicity does not resolve to meet eligibility or baseline parameters within 14 days of drug discontinuation, the patient must be removed from protocol therapy.

6.2.3 If the same dose-limiting toxicity recurs in a patient who has resumed treatment at the reduced dose level, the patient must be removed from protocol therapy.

# 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. Careful monitoring of electrolytes for hypophosphatemia and other electrolyte imbalances during treatment with entinostat is recommended and electrolyte supplementation may be warranted. See COG Supportive Care Guidelines at https://childrensoncologygroup.org/index.php/cog-supportive-care-guidelines. See Section 4.2.2 for drugs that should not be used concomitantly with entinostat.

## 7.4 Growth Factors

Growth factors that support platelet or white cell number or function are not allowed.

## 7.5 Concomitant Medications

Concurrent therapy with valproic acid is not allowed for patients receiving study drug.

# 8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

## 8.1 Required Clinical, Laboratory and Disease Evaluation

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

| STUDIES TO BE OBTAINED | Pre-Study | During Cycle 1 | Prior to Subsequent Cycles^ |
|---|---|---|---|
| History | X | Weekly | X |
| Physical Exam with vital signs | X | Weekly | X |
| Height, weight, BSA | X | | X |
| Performance Status | X | | |
| CBC, differential, platelets | X | Twice Weekly | Weekly[3] |
| Pharmacokinetics[1] | X | X | X |
| Urinalysis | X | | |
| Electrolytes including $Ca^{2+}$, $PO_4^{3-}$, $Mg^{2+}$; glucose | X | Weekly | X |
| Creatinine, ALT, bilirubin | X | Weekly | X |
| Albumin | X | | X |
| Tumor Disease Evaluation | X | End of Cycle 1 | Every other cycle x 2 then q 3 cycles[4] |
| Pharmacodynamics Studies (H3 and H4 Histone Acetylation in PBMCs)[6] | X | X[7] | |
| Pregnancy Test[2] | X | | |
| Patient Diary[5] | | Weekly | X |

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

1 See Section 8.3 for timing of PK studies.

2 Women of childbearing potential require a negative pregnancy test prior to starting treatment; sexually active patients must use an acceptable method of birth control. Abstinence is an acceptable method of birth control. Patients of reproductive potential must use secure methods of contraception during treatment and for 3 additional months after the end of treatment. Those who become pregnant while on treatment with entinostat must discontinue immediately and consult their treating physician.

3 If patients develop Grade 4 neutropenia or Grade 4 thrombocytopenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3.

4 Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Subsequent scans may restart 2 cycles after the confirmatory scan. Please note that for solid tumor patients, if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically.

5 Patient diary (see Appendix V) should be reviewed after completion of each treatment cycle and uploaded into RAVE. During Cycle 1, patient diary should be reviewed weekly and uploaded into RAVE.

6 These blood draws will only occur in patients who consent to this optional component of the study.

7 See Section 8.4 for timing of the pharmacodynamics studies.

## 8.2 Radiology Studies

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

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the ImageInBox.
COG institutions that are not connected via the ImageInBox can send the images on CD ROM or USB flash drive. Submitted imaging studies should be clearly marked with the COG patient ID, study number (STUDY #ADVL1513) and date and shipped to Syed Aamer at the address below:

Syed Aamer, MBBS, CRP
Administrator, Imaging Research Center
Children's Hospital Los Angeles
4650 Sunset Boulevard, MS # 81
Los Angeles, CA 90027
[redacted]

## 8.3 Pharmacology (required)

### 8.3.1 Description of Studies and Assay

Pharmacokinetics (PK) will be performed to determine the PK of entinostat in children. Pharmacokinetic analysis will be conducted at a centralized laboratory using validated assays.

### 8.3.2 Sampling Schedule (See Appendix VI)

Blood samples will be obtained prior to drug administration and at the following time points:

- **Day 1 of Cycle 1:** pre-dose, and at 0.5, 1, 3, 6, 24 (Day 2), and 48 to 96 hours post-dose.
- **Day 8 of Cycle 1**: pre-dose.
- **Day 22 of Cycle 1**: pre-dose, 1 hour post-dose.
- **Day 28 of Cycle 1**: prior to Day 1, Cycle 2 dose.

### 8.3.3 Sample Collection and Handling Instructions

Blood samples (3 ml) will be collected in specified collection tubes according to the lab manual. Sample kits with pre-printed labels will be provided by Covance.

### 8.3.4 Sample Processing

Samples will be processed according to the lab manual.

### 8.3.5 Sample Labeling

Each tube must be labeled with the patient's COG patient ID number. If not using pre-printed labels, they must also be labeled with the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the samples. Sample kits with pre-printed labels will be provided by Covance.

### 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 Pharmacodynamic Studies (optional)

### 8.4.1 Description of Studies

In consenting patients, exploratory pharmacodynamic assessment of histone H3 and H4 acetylation will be performed in PBMCs to evaluate the change in acetylation after administration of entinostat as a potential biomarker of HDAC inhibition.

### 8.4.2 Sampling Schedule (See Appendix VII)

Whole blood specimens (3 ml) will be collected from all consenting patients at:

- **Day 1 of Cycle 1:** pre-dose, and at 6 and 24 (Day 2) hours post-dose.
- **Day 8 of Cycle 1:** pre-dose.

### 8.4.3 Sample Collection and Handling Instructions

Blood samples (3 ml) will be collected in CPT tubes for pharmacodynamic evaluation according to the lab manual. Record the exact time that the sample is drawn along with the exact time that the drug is administered. Sample kits with pre-printed labels will be provided by Covance.

### 8.4.4 Sample Processing

- Samples will be processed according to the lab manual.
- During blood draw, fill tube with blood as completely as possible. Mix the blood in the vacutainer tube by gently inverting the tube 6 to 8 times.
- Keep all samples refrigerated from the moment of drawing until shipment.

### 8.4.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Pharmacodynamics Study Form, which must accompany the sample(s). Sample kits with pre-printed labels will be provided by Covance.

### 8.4.6 Sample Shipping Instructions

- Keep all samples refrigerated from the moment of drawing until shipment.
- Samples must be shipped THE SAME DAY as blood is taken using overnight shipping. If possible, schedule of treatment should be planned to avoid sending samples on Fridays and Saturdays.
- Sample tubes should be placed in a plastic bag and preferably be packed with a cold pack (like U-tek -1ºC/+30ºF Tegrant Corporation cold pack) rather than a frozen ice pack. To minimize any movement during transit and prevent damage of blood cells, the plastic bag with tubes must be properly insulated from the cold pack with packing material (bubble wrap, paper towels, crumpled paper, etc.) and placed on the cold pack (not

between bottom of the box and pack or between 2 cold packs) so that tubes do not touch the pack. Please avoid using wet ice, as accidental contact with water will break down blood cells. Please also fill any empty space in the package with packing material.

- Refer to instructions in the lab manual.
- Include Appendix VII, Pharmacodynamic Study Form, with the shipment
- Ship samples to the following address:

Trepel Laboratory
CCR, NCI, NIH
10 Center Drive
Building 10, Clinical Center, Room 12C208
Bethesda, MD 20892
[redacted]

## 9.0 AGENT INFORMATION

### 9.1 Entinostat

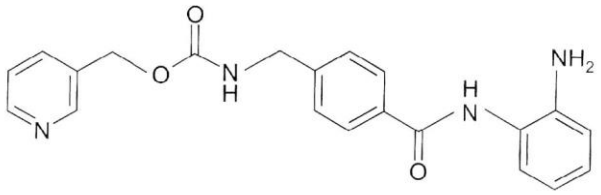
**(SNDX-275, MS-275,** NSC#706995, [redacted]), NCI-supplied agent

#### 9.1.1 Structure and molecular weight

**Chemical name:** 3-Pyridylmethyl N-{4-[(2-aminophenyl)carbamoyl]benzyl}carbamate

**Molecular formula:** $C_{21}H_{20}N_4O_3$

**Structural formula:**




**Molecular weight:** 376.41

**Mechanism of action:** Entinostat inhibits to a family of enzymes called histone deacetylases (HDACs) that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones. Entinostat inhibits histone deacetylases, changes chromatin configuration, and induces differentiation and apoptosis of cancer cells through an epigenetic mechanism.

#### 9.1.2 Supplied by:

Entinostat is supplied by Syndax Pharmaceuticals, Inc. and distributed by DCTD, NCI.

9.1.3 Formulation

The agent is supplied as a 1 mg (pink to light red, in bottles of 40), or 5 mg (yellow, in bottles of 40) film-coated tablets (round-biconvex). Each tablet also contains mannitol, carboxymethyl starch sodium, hydroxypropyl cellulose, potassium bicarbonate, and magnesium stearate. The film coating consists of hydroxypropyl methylcellulose, talc, titanium dioxide, and ferric oxide pigments (red and yellow).

9.1.4 Storage

Store the bottles at room temperature (15-30ºC), and protect from light. Tablets may be dispensed in pharmacy amber dispensing bottles with storage at a temperature equal or below 15-30°C (59-86°F; do not freeze) with an expiration period of 30 days from the date of repackaging.

9.1.5 Stability

Shelf life stability studies of the intact bottles are on-going. Tablets dispensed in pharmacy amber dispensing bottles should have an expiration date of 30 days from the date of repackaging.

9.1.6 Administration

Administer orally, on an empty stomach, at least 1 hour before or 2 hours after a meal. Tablets should be swallowed whole and not split, crushed or chewed. If a patient vomits within 30 minutes after the dose of entinostat is administered, that dose may be repeated. If the patient vomits more than 30 minutes after administration of entinostat, the dose will be considered as having been taken, and administration should resume with the subsequent regularly scheduled dose.

9.1.7 Drug interactions

No formal drug interaction studies have been performed in humans.
Data from in vitro experiments showed that, while entinostat inhibited cytochrome P-450 enzymes 2B6 and 3A4, the degree of the inhibition make it unlikely that any *in vivo* systemic interactions would occur. Intestinal CYP 3A4 may be inhibited by entinostat. However, entinostat did not inhibit any UGT enzymes tested. In addition, entinostat was found to induce CYP 1A2, CYP 2C6, and CYP 2B8 as well as UGT 1A4. Finally, entinostat is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) transporters.

9.1.8 Entinostat Toxicities

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 215 patients.* Below is the CAEPR for MS-275 (SNDX-275, entinostat).

**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 2.5, September 10, 2018[1]**

| Adverse Events with Possible Relationship to MS-275 (SNDX-275, entinostat) (CTCAE 5.0 Term) [n= 221] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| Anemia | | | ***Anemia (Gr 3)*** |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | ***Abdominal pain (Gr 2)*** |
| | Constipation | | ***Constipation (Gr 2)*** |
| | Diarrhea | | ***Diarrhea (Gr 3)*** |
| | Dyspepsia | | ***Dyspepsia (Gr 2)*** |
| Nausea | | | ***Nausea (Gr 3)*** |
| Vomiting | | | ***Vomiting (Gr 3)*** |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Edema limbs | | ***Edema limbs (Gr 2)*** |
| Fatigue | | | ***Fatigue (Gr 3)*** |
| | Fever | | ***Fever (Gr 2)*** |
| INFECTIONS AND INFESTATIONS | | | |
| | Infection[2] | | ***Infection[2] (Gr 3)*** |
| INVESTIGATIONS | | | |
| | Alkaline phosphatase increased | | ***Alkaline phosphatase increased (Gr 2)*** |
| | Lymphocyte count decreased | | ***Lymphocyte count decreased (Gr 4)*** |
| Neutrophil count decreased | | | ***Neutrophil count decreased (Gr 4)*** |
| Platelet count decreased | | | ***Platelet count decreased (Gr 4)*** |
| | White blood cell decreased | | ***White blood cell decreased (Gr 3)*** |
| METABOLISM AND NUTRITION DISORDERS | | | |
| Anorexia | | | ***Anorexia (Gr 3)*** |
| | Dehydration | | ***Dehydration (Gr 2)*** |
| | Hyperglycemia | | ***Hyperglycemia (Gr 2)*** |

| Adverse Events with Possible Relationship to MS-275 (SNDX-275, entinostat) (CTCAE 5.0 Term) [n= 221] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| Hypoalbuminemia | | | ***Hypoalbuminemia (Gr 2)*** |
| | Hypocalcemia | | ***Hypocalcemia (Gr 2)*** |
| | Hypokalemia | | ***Hypokalemia (Gr 2)*** |
| | Hyponatremia | | ***Hyponatremia (Gr 3)*** |
| Hypophosphatemia | | | ***Hypophosphatemia (Gr 3)*** |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Myalgia | | ***Myalgia (Gr 2)*** |
| NERVOUS SYSTEM DISORDERS | | | |
| | Dysgeusia | | ***Dysgeusia (Gr 2)*** |
| Headache | | | ***Headache (Gr 2)*** |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Cough | | ***Cough (Gr 2)*** |
| | Dyspnea | | ***Dyspnea (Gr 3)*** |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | | Erythema multiforme | |

[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]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATION SOC.

[3]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.

**Adverse events reported on MS-275 (SNDX-275, entinostat) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that MS-275 (SNDX-275, entinostat) caused the adverse event:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Febrile neutropenia; Hemolysis; Leukocytosis
**CARDIAC DISORDERS** - Atrial fibrillation; Atrioventricular block complete; Cardiac disorders - Other (transient right-side heart failure with worsening tricuspid regurgitation); Chest pain - cardiac; Conduction disorder; Heart failure; Left ventricular systolic dysfunction; Palpitations; Pericardial effusion; Pericarditis; Sinus tachycardia; Supraventricular tachycardia; Ventricular fibrillation
**EAR AND LABYRINTH DISORDERS** - Hearing impaired
**EYE DISORDERS** - Blurred vision
**GASTROINTESTINAL DISORDERS** - Anal mucositis; Colitis; Dysphagia; Enterocolitis; Esophageal pain;

Esophagitis; Flatulence; Gastrointestinal disorders - Other (hyperdefecation); Gastrointestinal hemorrhage[3]; Hemorrhoids; Mucositis oral; Pancreatitis; Periodontal disease; Rectal mucositis; Rectal pain; Small intestinal mucositis; Typhlitis; Visceral arterial ischemia
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema face; Generalized edema; Injection site reaction; Multi-organ failure; Non-cardiac chest pain; Pain
**IMMUNE SYSTEM DISORDERS** - Allergic reaction; Anaphylaxis; Autoimmune disorder
**INJURY, POISONING AND PROCEDURAL COMPLICATIONS** - Bruising
**INVESTIGATIONS** - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Creatinine increased; GGT increased; INR increased; Investigations - Other (coagulopathy); Investigations - Other (vitamin D deficiency); Lipase increased; Serum amylase increased; Weight loss
**METABOLISM AND NUTRITION DISORDERS** - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypertriglyceridemia; Hyperuricemia; Hypoglycemia; Hypomagnesemia; Tumor lysis syndrome
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Arthralgia; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Muscle cramp; Musculoskeletal and connective tissue disorder - Other (thorax pain); Myositis; Pain in extremity
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor pain
**NERVOUS SYSTEM DISORDERS** - Ataxia; Depressed level of consciousness; Dizziness; Dysphasia; Intracranial hemorrhage; Neuralgia; Olfactory nerve disorder; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Syncope; Tremor
**PSYCHIATRIC DISORDERS** - Anxiety; Confusion; Depression; Insomnia; Libido decreased
**RENAL AND URINARY DISORDERS** - Acute kidney injury; Proteinuria; Renal and urinary disorders - Other (bladder distension); Renal calculi; Renal hemorrhage; Urinary frequency; Urinary retention
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Allergic rhinitis; Atelectasis; Epistaxis; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pleuritic pain; Pulmonary edema; Respiratory failure; Tracheal mucositis
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Hyperhidrosis; Nail loss; Photosensitivity; Pruritus; Purpura; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (hyperkeratotic lesions/squamous cell carcinoma); Urticaria
**SURGICAL AND MEDICAL PROCEDURES** - Surgical and medical procedures - Other (packed RBC transfusion)
**VASCULAR DISORDERS** - Flushing; Hypertension; Hypotension; Thromboembolic event

**Note**: MS-275 (SNDX-275, entinostat) 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.

### 9.2 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.

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, and 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.

In general, sites may order initial agent supplies when a subject is being screened for enrollment onto the study.

### 9.3 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 Oral 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.

### 9.4 Investigator Brochure Availability

The current versions 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.

### 9.5 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)

# 10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

## 10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease (See Section 12.0).
b) Adverse Events requiring removal from protocol therapy (See Section5_2Section 6.0).
c) Refusal of protocol therapy by patient/parent/guardian
d) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
e) Physician determines it is not in the patient's best interest.
f) 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 entinostat (See Section 8.1).
g) Study is terminated by Sponsor.
h) Pregnancy.

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

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

## 10.2 Off Study Criteria

a) Thirty days after the last dose of the investigational agent.
b) Death
c) Lost to follow-up
d) Withdrawal of consent for any required observations or data submission.
e) Enrollment onto another COG therapeutic (anti-cancer) study
f) The fifth anniversary of the date the patient was enrolled on this study.
g) The patient does not receive protocol treatment after study enrollment.

# 11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

## 11.1 Sample Size and Study Duration

A minimum of 4 patients will be enrolled in this study. The expected maximum number of evaluable patients required to estimate the MTD/RP2D is 12. Once the MTD or recommended Phase 2 dose has been defined, up to 6 additional patients with recurrent or refractory solid tumors may be enrolled to acquire PK data in a representative number of young patients (i.e. patients < 12 years old). Therefore, a maximum of 22 patients are expected to be enrolled which allows for 6 patients at each of 2 dose levels, 6 additional patients enrolled at the MTD/RP2D for PK analysis, and a 20% inevaluable rate. 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 11-22 months. An absolute maximum of 36 patients is anticipated in the unlikely scenario that each of 2 dose levels is expanded to 12 patients due to different classes of AEs, 6 additional patients are enrolled at the MTD for PK analysis, and a 20% inevaluable rate. The absolute maximum would require about 18-36 months for completion.

## 11.2 Definitions

### 11.2.1 Evaluable For Adverse Events

Any patient who receives at least one dose of the study drug(s) and who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-escalation portion during Cycle 1, patients must receive 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 5.5) during Cycle 1 of therapy.

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

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

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

- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the

dose escalation portion of the study. If ≥ 1/3 of the cohort of patients at the MTD (during the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

### 11.3 Dose Escalation and Determination of MTD

The rolling six phase 1 trial design will be used for the conduct of this study.[32] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

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

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

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

| | | | | |
|---|---|---|---|---|
| 5 | 1 | 0, 1, 2, 3 or 4 | 0, 1, 2, 3 or 4 | Same dose level |
| 5 | 0 | 5 | 0 | Escalate** |
| 5 | ≥ 2 | 0, 1, 2 or 3 | 0, 1, 2 or 3 | De-escalate* |
| 6 | 0 | 0, 1, 2, 3, or 4 | 2, 3, 4, 5 or 6 | Suspend |
| 6 | 1 | 0, 1, 2, 3 or 4 | 0, 1, 2, 3 or 4 | Suspend |
| 6 | 0 or 1 | 5 or 6 | 0 or 1 | Escalate** |
| 6 | ≥ 2 | 0, 1, 2, 3 or 4 | 0, 1, 2, 3 or 4 | De-escalate* |

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

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

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

## 11.4 Inclusion of Children, Women and Minorities

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

The gender and minority distribution of the study population is projected to be[1]:

| 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 | 1 | 1 | 0 | 0 | **2** |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 | 0 | **0** |

[1]These distributions are based on historical Phase 1 enrollments.

| Racial Categories | Ethnic Categories | | | | Total |
|---|---|---|---|---|---|
| | Not Hispanic or Latino | | Hispanic or Latino | | |
| | Female | Male | Female | Male | |
| Black or African American | 2 | 4 | 0 | 0 | **6** |
| White | 9 | 15 | 2 | 1 | **27** |
| More Than One Race | 1 | 0 | 0 | 0 | **1** |
| **Total** | **13** | **20** | **2** | **1** | **36** |

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### 11.5 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of entinostat 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 entinostat, patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors, and will be reported descriptively.

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

## 12.0 EVALUATION CRITERIA

### 12.1 Common Terminology Criteria for Adverse Events (CTCAE)

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

### 12.2 Response Criteria for Patients with Solid Tumors

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

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1).[34] Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

12.2.1 Definitions

12.2.1.1 Evaluable for objective response: Patients who exhibit objective disease progression prior to the end of cycle 1 will be considered evaluable for response. For all other patients, only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response.

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

12.2.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area must show definitive evidence of progression to be considered measurable.

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

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

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

12.2.2.4 Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

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

12.2.3 Methods for Evaluation of Measurable Disease

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

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

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

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

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

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

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

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

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

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of

disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

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

### 12.2.4 Response Criteria for Patients with Solid Tumor and Measurable Disease

#### 12.2.4.1 **Evaluation of Target Lesions**

Complete Response (CR): Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma).

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as

reference the smallest sum diameters while on study

#### 12.2.4.2 **Evaluation of Non-Target Lesions**

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

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

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

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

### 12.2.5 Overall Response Assessment

Table 1: For Patients with Measurable Disease (i.e., Target Disease)

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

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

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

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

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

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

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

#### 12.2.6 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.6 from a sequence of overall response assessments.

### 12.3 Response Criteria for Patients with Solid Tumors and Evaluable Disease

#### 12.3.1 Evaluable Disease

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

#### 12.3.2 Complete Response

Disappearance of all evaluable disease.

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

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

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

12.3.6 Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.6 from a sequence of overall response assessments.

## 12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

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

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

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

12.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale14 as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2 for details on transferring images to the Imaging Research Center.

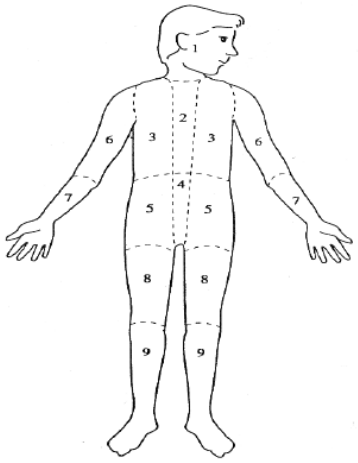
NOTE: This scoring should also be done by the treating institution for end of course response assessments.

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

0 = no site per segment,

1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

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




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

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

### 12.4.4 Overall Response Assessment

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

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

| MIBG | CT/MRI | Bone Scan | Bone Marrow | Catechol | Overall |
|---|---|---|---|---|---|
| PD | Any | Any | Any | Any | PD |

| | | | | | |
|---|---|---|---|---|---|
| Any | New Lesion | Any | Any | Any | PD |
| Any | Any | PD | Any | Any | PD |
| Any | Any | Any | PD | Any | PD |
| SD | No New Lesion | Non-PD | Non-PD | Any | SD |
| PR | No New Lesion | Non-PD | Non-PD | Any | PR |
| CR | No New Lesion | Non-PD | Non-PD | Elevated | PR |
| CR | No New Lesion | CR | CR | Normal | CR |

12.4.5 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 3 in Section 12.6.

## 12.5 Response Criteria for Patients with CNS Tumors

12.5.1 Measurable Disease

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

12.5.2 Evaluable Disease

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

12.5.3 Selection of Target and Non-Target Lesions

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

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

12.5.4 Response Criteria for Target Lesions

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

- **Complete Response (CR):** Disappearance of all target lesions.

- **Partial response (PR):** ≥ 50% decrease in the sum of the products of the two perpendicular diameters of all target lesions (up to 5), taking as reference the initial baseline measurements.

- **Stable Disease (SD):** Neither sufficient decrease in the sum of the products of the two perpendicular diameters of all target lesions to qualify for PR, nor sufficient increase in a single target lesion to qualify for PD.

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

12.5.5 Response Criteria for Non-Target Lesions:

- **Complete Response (CR):** Disappearance of all non-target lesions.

- **Incomplete Response/Stable Disease (IR/SD):** The persistence of one or more non-target lesions.

- **Progressive Disease (PD):** The appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

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

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

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

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.6 from a sequence of overall response assessments.

## 12.6 Best Response

### 12.6.1 Evaluation of Best Overall Response

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

Table 3. Sequences of overall response assessments with corresponding best response.

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

### 12.6.2 Duration of Response

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

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

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

## 13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the Case Report Forms for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

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

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

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

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

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP 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.

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

- 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.

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

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

- Grade 1 and 2 adverse events listed in the table below do **not** require expedited reporting via CTEP-AERS:

| Category | Adverse Events |
|---|---|
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | Febrile neutropenia |
| GASTROINTESTINAL DISORDERS | Flatulence |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | Non-cardiac chest pain |
| INVESTIGATIONS | Alanine aminotransferase increased |
| | Aspartate aminotransferase increased |
| | Blood bilirubin increased |
| | Creatinine increased |

| | |
|---|---|
| | Weight loss |
| METABOLISM AND NUTRITION DISORDERS | Hypomagnesemia |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | Arthralgia |
| | Back pain |
| | Generalized muscle weakness |
| | Pain in extremity |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | Epistaxis |

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.8 of the protocol. Additional protocol-specific exceptions to expedited reporting of serious adverse events are the toxicities in bold font listed under the drug information section of the protocol (Section 9.1).

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 at 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# 301-230-0159) and by email to the ADVL1513 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.

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 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 ADVL1513 COG Study Assigned Research Coordinator along with any additional medical information. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

### 13.7.1 Pregnancy

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

### 13.7.2 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.

13.7.3 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. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf.

## 14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

### 14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: Roadmaps, 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 CDUS data will be submitted quarterly to CTEP by electronic means. Reports are

due January 31, April 30, July 31 and October 31. **Note**: If this study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting guidelines must be reported via the monitoring method identified above. If this study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS.
This is not a responsibility of institutions participating in this trial.

### 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.

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## APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

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

# APPENDIX II: CORRELATIVE STUDIES GUIDE

| Correlative Study | Appendix | Sample Volume | | Tube Type |
|---|---|---|---|---|
| | | Volume per sample | Total Cycle 1 | |
| Pharmacokinetic Study | VI | 3 ml | 33 ml | heparin tubes (green top) |
| Pharmacodynamic Study (PBMCs) | VII | 3 ml | 12 ml | CPT tubes |
| **Total Blood Volume** | | | **45 ml** | |

## APPENDIX III: TOXICITY-SPECIFIC GRADING

Bilirubin

| | |
|---|---|
| Grade 1: | ≤ 1.5 x ULN |
| Grade 2: | > 1.5- 3.0 x ULN |
| Grade 3: | > 3.0-10.0 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: | ≤ 135 |
| Grade 2: | 136- 225 |
| Grade 3: | 226- 900 |
| Grade 4: | > 900 |

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

| | |
|---|---|
| Grade 1: | ≤ 150 |
| Grade 2: | 151-250 |
| Grade 3: | 251-1000 |
| Grade 4: | > 1000 |

GGT:

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

# APPENDIX IV: ENTINOSTAT DOSING NOMOGRAM

**Entinostat Dose Assignment: 1.6 mg/m$^2$**
**(Dose Modification for DLT at Dose Level -1)**

| BSA (m$^2$) | Total Weekly Dose (mg) |
|---|---|
| 1.17-1.56 | 2 |
| 1.57-2.18 | 3 |
| 2.19-2.30 | 4 |
| >2.30 | 4 |

**Entinostat Dose Assignment: 2.3 mg/m$^2$**
**(Dose Level -1)**

| BSA (m$^2$) | Total Weekly Dose (mg) |
|---|---|
| 1.17-1.52 | 3 |
| 1.53-1.95 | 4 |
| 1.96-2.30 | 5 |
| >2.30 | 5 |

**Entinostat Dose Assignment: 3 mg/m$^2$**
**(Dose Level 1)**

| BSA (m$^2$) | Total Weekly Dose (mg) |
|---|---|
| 1.17-1.50 | 4 |
| 1.51-1.83 | 5 |
| 1.84-2.16 | 6 |
| 2.17-2.30 | 7 |
| >2.30 | 7 |

**Entinostat Dose Assignment: 4 mg/m$^2$**
**(Dose Level 2)**

| BSA (m$^2$) | Total Weekly Dose (mg) |
|---|---|
| 1.17-1.37 | 5 |
| 1.38-1.62 | 6 |
| 1.63-1.87 | 7 |
| 1.88-2.12 | 8 |
| 2.13-2.30 | 9 |
| >2.30 | 9 |

# APPENDIX V: ENTINOSTAT TABLETS PATIENT DIARY

**COG Patient ID:_____ ACC # : _____ Institution :_____ BSA:_____ m²**
***Please do not write patient names on this form.***

**Instructions:** Complete the diary below by recording the date and time the dose of entinostat is given as well as the number and tablet strengths (1 mg or 5 mg) of tablets taken for each dose. **Make note of other drugs and supplements taken in the Comments section of the diary.**
Entinostat should be given once a week.
**If you vomit within 30 minutes after taking entinostat, that dose may be repeated. If you vomit greater than 30 minutes after taking entinostat, the dose will not be repeated. Administration should resume with the next regularly scheduled dose.** Record this event in the diary and continue on the normal dosing schedule. If you miss an entinostat dose and less than 12 hours have passed since the scheduled dosing time, that dose should be taken immediately. If you miss an entinostat dose and more than 12 hours have passed since the scheduled dosing time, skip that dose and continue on the normal dosing schedule. If you accidently take an extra dose during a day, skip the next scheduled dose of entinostat.
Return the completed diary and all study medication bottles to the study clinic at each visit (weekly during Cycle 1 and then after each treatment cycle). The study clinic will submit this diary into an electronic system to record the information.

*EXAMPLE*

| *WEEK 1* | *Date* | *Time* | | *# of entinostat tablets prescribed to take* | | | *Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)* |
|---|---|---|---|---|---|---|---|
| | | | | *mg* | *mg* | *mg* | |
| | | | | *AM# PM#* | *AM# 3 PM#* | *AM# PM#* | |
| | | | | *# of entinostat tablets taken* | | | |
| | | | | *mg* | *mg* | *mg* | |
| *Day 1* | *03/11/16* | *8.30* | *AM* | | *3* | | *He felt nauseated an hour after taking the drug but did not vomit.* |
| | | | *PM* | | | | |

**Cycle #: _____ Start Date: |__/__|__/__|__/__|**
**End Date: | / | / | / | Dose Level: _____mg/m²/dose**

| **WEEK 1** | **Date** | **Time** | | **# of entinostat tablets prescribed to take** | | | **Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)** |
|---|---|---|---|---|---|---|---|
| | | | | **1 mg** | **5 mg** | | |
| | | | | **AM / PM #___** | **AM / PM #___** | | |
| | | | | **# of entinostat tablets taken** | | | |
| | | | | **1 mg** | **5 mg** | | |
| **Day 1** | | | **AM / PM** | | | | |
| **WEEK 2** | **Date** | **Time** | | **# of entinostat tablets taken** | | | **Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)** |
| | | | | **1 mg** | **5 mg** | | |
| **Day 8** | | | **AM / PM** | | | | |
| **WEEK 3** | **Date** | **Time** | | **# of entinostat tablets taken** | | | **Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)** |
| | | | | **1 mg** | **5 mg** | | |
| **Day 15** | | | **AM / PM** | | | | |
| **WEEK 4** | **Date** | **Time** | | **# of entinostat tablets taken** | | | **Comments (Describe any missed or extra doses, vomiting and/or bothersome effects.)** |
| | | | | **1 mg** | **5 mg** | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Day 22** | | | **AM / PM** | | | | |

# APPENDIX VI: PHARMACOKINETIC 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: _____$m^2$

Entinostat Dose Level: _____$mg/m^2$ Entinostat Total Daily Dose: _____mg

Blood samples (3 ml) will be collected in preservative-free heparin (green-top) tubes at the following time points (± 10 min): Day 1 (pre-dose, 0.5 hr, 1 hr, 3 hrs, and 6 hrs after dose); Day 2 (24 [±2] hrs after Day 1 dose); Day 3-5 (48-96 hrs after Day 1 dose), Day 8 (pre-dose), Day 22 (pre-dose, 1 hr post-dose), and Day 28 of Cycle 1.

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

| Blood Sample No. | Time Point | Scheduled Collection Time | Actual Date Sample Collected | Actual Time Sample Collected (24-hr clock) |
|---|---|---|---|---|
| **1** | **Day 1** | Prior to entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **Entinostat Dose on Day 1 Date:**___/___/___ **Time:** \|__\|__\| : \|__\|__\| | | | | |
| **2** | **Day 1** | 0.5 hrs after entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **3** | **Day 1** | 1 hr after entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **4** | **Day 1** | 3 hrs after entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **5** | **Day 1** | 6 hrs after entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **6** | **Day 2** | 24 (±2) hrs after Day 1 entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **7** | **Day 3-5** | 48-96 hrs after Day 1 entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **8** | **Day 8** | Prior to entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **Entinostat Dose on Day 8 Date:**___/___/___ **Time:** \|__\|__\| : \|__\|__\| | | | | |
| **Entinostat Dose on Day 15 Date:**___/___/___ **Time:** \|__\|__\| : \|__\|__\| | | | | |
| **9** | **Day 22** | Prior to entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **10** | **Day 22** | 1 hr after entinostat dose | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **Entinostat Dose on Day 22 Date:**___/___/___ **Time:** \|__\|__\| : \|__\|__\| | | | | |
| **11** | **Day 28*** | Prior to beginning Cycle 2 | ___/___/___ | \|__\|__\| : \|__\|__\| |

*Patients who are removed from therapy during Cycle 1 after receiving the dose on Day 22 should still have the Day 28 sample collected.

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 8.3.6. See Section 8.3 for detailed guidelines for packaging and shipping PK samples.

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

## APPENDIX VII: PHARMACODYNAMIC STUDY FORM

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

Body Surface Area: _____$m^2$ Dose Level: _____$mg/m^2$ Entinostat Total Daily Dose: _____mg

In consenting patients, blood samples (3 ml) will be collected in CPT tubes at the following time points (± 10 min): Day 1 (pre-dose, 6 hrs post-dose), Day 2 (24 [±2] hrs after Day 1 dose), and Day 8 (pre-dose) of Cycle 1.

Record the exact time the sample is drawn along with the exact time entinostat is given on Days 1 and 8.

| Blood Sample No. | Time Point | Scheduled Collection Time | Actual Date Sample Collected | Actual Time Collected (24-hr clock) |
|---|---|---|---|---|
| 1 | Cycle 1, Day 1 | prior to entinostat dose | | \|__\|__\| : \|__\|__\| |
| **Entinostat Dose on Day 1 Date:___/___/___ Time: \|__\|__\| : \|__\|__\|** | | | | |
| 2 | Cycle 1, Day 1 | 6 hrs after entinostat dose | | \|__\|__\| : \|__\|__\| |
| 3 | Cycle 1, Day 2 | 24 (±2) hrs after Day 1 entinostat dose | | \|__\|__\| : \|__\|__\| |
| 4 | Cycle 1, Day 8 | prior to entinostat dose | | \|__\|__\| : \|__\|__\| |
| **Entinostat Dose on Day 8 Date:___/___/___ Time: \|__\|__\| : \|__\|__\|** | | | | |

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 samples.

Record any notes for Sample Storage Conditions below.

**Notes:** _____

_____

_____

_____

_____

_____

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

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

## APPENDIX VIII: ISOLATION OF PBMCS AND PLASMA FOR CORRELATIVE STUDIES

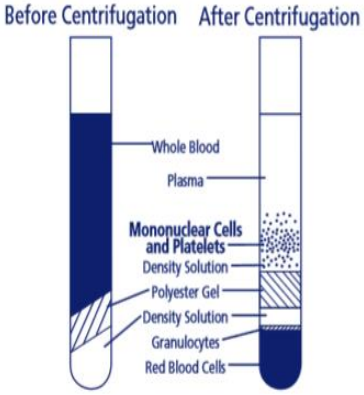
### Isolation and Storage of Peripheral Blood Mononuclear Cells (PBMCs)

a) Purpose

To isolate Peripheral Blood Mononuclear Cells (PBMCs) for long term storage.

b) Equipment and Material Required

- Whole blood samples to be processed (freshly collected into CPT)
- Cell preparation tubes (CPT)
- Centrifuge (capable of centrifugation at 1,600 × rcf)
- Pipette and tips
- 0.5 and 2.0 ml cryo tubes (capable of being stored at -80˚C or -150˚C)
- Extra collection tubes (to counterbalance during centrifugation)
- 1 x PBS (room temperature)




c) Procedure

1. Gently invert CPT tubes 5 times before placing in the centrifuge
2. Counter balance extra collection tubes for centrifugation
3. Centrifuge the samples for 20 minutes at 1,600 × rcf at room temperature

   ***Ensure that tubes will not hit inside of centrifuge rotor once centrifugation begins
4. Remove tubes from centrifuge, ensuring that tubes are kept in the upright position so as not to disturb layers.
5. Aliquot plasma into labeled 2 ml aliquots, as appropriate (see SOP Processing Blood Samples Step 4 - 5)

   ***Be careful not to disrupt the cell layer while aspirating plasma (see image above)
6. Transfer small amount of remaining plasma and cells from CPT tubes into a 15 ml conical tube

7. Rinse CPT tubes using 5 ml of 1 × PBS (gently pipette up and down)

   ***Be careful not to disturb the gel matrix. Rinsing should remove most of the cells from the gel matrix. The wash may be reddish in color.

8. Transfer the rinse mixture into the same 15 ml conical tube (one tube per patient sample)
9. Discard the rinsed CPT tubes in the biohazard waste
10. Bring the total volume, in the 15 ml conical tube, to 15 ml using 1 × PBS
11. Mix the cells by gently inverting the tube 5 times
12. Centrifuge at 300 × rcf for 15 minutes at room temperature
13. Aspirate and discard the supernatant, being careful not to disturb the cell pellet
14. Add 200-500 µl of PBS to the cell pellet and pipette gently to resuspend pellet (use smallest volume of PBS to fully resuspend pellet)
15. Aliquot resuspended cells into 0.5 ml labeled cryo tubes and place in -80˚C freezer

## APPENDIX IX: 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 >. **Error! Hyperlink reference not valid.**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 ADVL1513 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.