A PHASE 2 SINGLE-ARM MULTI-CENTER STUDY OF ENTINOSTAT IN PATIENTS WITH RELAPSED OR REFRACTORY ABDOMINAL NEUROENDOCRINE TUMORS

NCT03211988

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Study Supporters:	Syndax Pharmaceuticals, Inc. Falconwood Foundation
Date:	May 19th 2020

INVESTIGATOR'S AGREEMENT

I have read the attached protocol entitled "A Phase 2 Single-Arm Multi-Center Study of Entinostat in Patients with Relapsed or Refractory Abdominal Neuroendocrine Tumors", dated November 11, 2019, and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice and applicable regulations of the Food and Drug Administration.
I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my sub investigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Syndax.

Signature	Date
Name of Principal Investigator	

PROTOCOL SYNOPSIS

TITLE	A phase 2 single-arm multi-center study of entinostat in patients with relapsed or refractory abdominal neuroendocrine tumors
SCIENTIFIC HYPOTHESIS	It is hypothesized that entinostat will: • inhibit proliferation of a subset of abdominal neuroendocrine tumors with a signature transcriptional interactome • arrest tumor progression as evidenced by tumor shrinkage or stabilization in the study patient population.
OBJECTIVES	Primary Objective • Estimate the objective response rate (ORR) with entinostat in patients with relapsed or refractory abdominal neuroendocrine tumors. Objective response will include complete response (CR) and partial response (PR) and will be determined from each patient's best confirmed response during protocol therapy Secondary Objectives • Evaluate the duration of response for patients who achieve responses • Assess the duration of overall survival (OS) • Assess progression-free survival (PFS) • Safety Exploratory • Assess biologic markers including transcriptional interactomes and master regulators that may predict efficacy or toxicity of entinostat
STUDY DESIGN	Phase 2, multicenter, open label, single arm study. Eligible patients will be enrolled according to Simon's two-stage design as described below. Objective response to treatment will be assessed using RECIST criteria until progression or intolerable toxicities occur necessitating cessation of treatment.
STUDY POPULATION	Up to 40 patients with relapsed or refractory abdominal neuroendocrine tumors may be enrolled to achieve up to 32 response-evaluable patients. The study will enroll patients regardless of expression profile (unselected patients) to assess activity in this patient population. If the minimal level of activity is not seen following stage I, entinostat will be declared to have insufficient activity in this indication in unselected patients. Thereafter, enrollment will be restricted to patients whose tumors display the characteristic master regulator expression profile consistent with hypothesized entinostat sensitivity.
ELIGIBILITY CRITERIA	**Inclusion Criteria:** Patients must fulfill all of the following inclusion criteria in order to be admitted into the study: 1. Pathologically confirmed stage IV, unresectable relapsed, or unresectable refractory abdominal neuroendocrine tumor from the last biopsy available which may be the initial diagnostic biopsy.

ELIGIBILITY CRITERIA (cont'd)	*Relapsed disease is defined as progressive disease following systematic therapy with lanreotide or equivalent. Refractory disease is defined as disease not responding to or having progressed within 1 month of the last dose of most recent systemic therapy to include lanreotide. (Note, small cell carcinoma and large cell undifferentiated neuroendocrine tumors will be excluded from this trial).* 2. Eligibility for stage 2 of the study, if the extension stage is opened, will be determined by RNAseq analysis and master regulator profile of a single fresh needle biopsy specimen obtained during study screening. 3. Documented disease that is radiographically measurable. 4. Last dose of prior therapy must be >14 days before the first dose of study drug administration. There is no upper limit to number of prior therapies. However, the patient must have recovered from acute toxicities from the most recent therapy to grade 1 or less. 5. ECOG performance status of 0 or 1 (must be done within 7 days prior to study drug administration). 6. Age 18 years or older 7. Total Bilirubin $\leq$ 1.5 x Upper Limit of Normal (ULN) and AST and ALT $\leq$ 2.5 x ULN (results within 7 days before study drug administration), ≤5×ULN for patients with liver metastases. 8. Serum creatinine $\leq$ 1.5 x ULN (results within 7 days before study drug administration) 9. Absolute neutrophil counts of $\geq$ 1500/μL (without growth factor support), platelet counts ≥100,000/μL (without transfusion support); and hemoglobin ≥9 g/dL results within 7 days before study drug administration. 10. Patients or their legal representative must be able to read, understand, and sign a written informed consent 11. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants AND Activated Partial Thromboplastin Time (aPTT) ≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants 12. If a female of childbearing potential, has a negative serum blood pregnancy test during screening and a negative urine pregnancy test within 3 days prior to receiving the first dose of study drug. If the screening serum test is done within 3 days prior to receiving the first dose of study drug, a urine test is not required. Note: Women of childbearing potential (WoCP) are any women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. WoCP include non-women who have experienced menopause onset < 12 months prior to enrollment. 13. If a female of childbearing potential, willing to use 2 methods of birth control or willing to abstain from heterosexual activity for the course of the study through 120 days after the last dose of study drug. 14. If male, agrees to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study drug.

	Exclusion Criteria Patients fulfilling any of the following criteria will not be admitted into the study: 1. Patients with another active cancer (excluding basal cell carcinoma or cervical intraepithelial neoplasia [CIN / cervical carcinoma in situ] or melanoma in situ). Prior history of other cancer is allowed, as long as there is no active disease within the prior 5 years. 2. Pregnant or lactating women. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test documented within 3 days prior to start of study drug. 3. Patients with uncontrolled intercurrent illness, active or uncontrolled infections, or a fever >38.5°C that has not been evaluated for infection up to the day of initial dosing. Patients with documented history of tumor fever are accepted provided acute or chronic infection has been excluded as possible cause of the fever. 4. Patients who have been treated with any investigational drug within 28 days prior to the first dose of study medication, or who are receiving concurrent treatment with other experimental drugs or anti-cancer therapy. 5. Prior treatment with HDAC inhibitors [e.g. valproic acid, vorinostat (Zolinza), romidepsin (Istodax)]. 6. History of pericarditis or pericardial effusion that had required medical or surgical intervention in the last 6 months, or myocardial infarction or arterial thromboembolic events within 6 months, or experiencing severe or unstable angina, or New York Heart Association (NYHA) Class III or IV disease, or a QTc interval >0.47 seconds 7. Known HIV or a history of active Hepatitis B or C as evidenced by laboratory abnormalities in addition to positive serology. Testing is not required for patients not suspected of having these conditions 8. Any condition (e.g., known or suspected poor compliance, psychological instability, geographical location, etc) that, in the judgment of the investigator, may affect the patient's ability to sign the informed consent and comply with study procedures 9. Any condition that will put the patient at undue risk or discomfort as a result of adherence to study procedures 10. Presence or history of brain metastases. 11. Uncontrolled hypertension or diabetes mellitus 12. Any contraindication to oral agents or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the investigator, would preclude adequate absorption. 13. Allergy to benzamide or inactive components of entinostat. 14. Patients may not be taking any corticosteroid for any reason while on study and all corticosteroids must be stopped two weeks prior to initiation of study drug.
STUDY TREATMENT	The dose of entinostat is 5 mg (one tablet) orally, once every week in a 28 day cycle. All patients will be treated until progression or intolerable toxicities occur.
ENDPOINTS	Primary Endpoint: • Objective response (CR or PR) based on the patient's best response that is documented during protocol therapy. Response will be assessed by RECIST criteria. Secondary Endpoints:

	• Duration of response for patients achieving CR or PR. • Overall survival • Progression-free survival • Duration of response for patients achieving PR or CR • Safety (Incidence, severity, and duration of adverse events, including serious adverse events and those considered by the investigator to be related to protocol therapy) Exploratory endpoints: • Change in transcriptional profile • Reduced expression of master regulators
SAMPLE SIZE	Up to 40 patients may be enrolled to achieve 32 response-evaluable patients. It's anticipated that no more than 25% of enrolled patients will be non-evaluable for response. The sample size for the expansion phase is based on a Simon 2-stage design (optimum version) and objective response rate endpoint described in Section 11.2. To calculate the required sample size, the following assumptions were made. The response probability of an ineffective therapy in this indication (i.e., the uninteresting response level) was chosen to be 15%; the response probability of an effective therapy (i.e., the targeted response level) was chosen to be at least 35%, level of significance of 10%, and power of 80%. Based on these assumptions, the sample size of the first and second stage is 9 and 14, respectively, for a total of 23 response-evaluable patients (see below). • If less than 2 of the 9 patients achieve an objective response (CR or PR) during the first stage of the study, enrollment will be terminated for unselected patients and entinostat will be declared to have insufficient activity in this indication in unselected patients. Thereafter, enrollment will be restricted to patients whose tumors display the characteristic master regulator expression profile consistent with hypothesized entinostat sensitivity. • If 6 or more unselected patients achieve objective response after completion of the second stage, then entinostat will be considered sufficiently promising in this treatment setting and may be evaluated in future studies. • If the total number of patients with objective response after completion of the second stage is between 2 and 5, further development of entinostat in this indication will be assessed. If the true objective response rate for entinostat is ≤ 15%, then the expected sample size is 14.61 patients, with probability of terminating the study at the end of the first stage equal to 60%. Up to 40 patients may be enrolled to achieve 32 response-evaluable patients (9 unselected patients in Stage 1, and 23 selected patients in Stages 1 and 2).
PROCEDURES	Schedule of Study Assessments is included in Appendix 1

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1. OBJECTIVES

1.1 Primary

The primary objective of this study is to estimate the objective response rate with entinostat in patients with relapsed or refractory abdominal neuroendocrine tumors. Objective response will include complete response (CR) and partial response (PR) and will be determined from each patient's best response that is documented during protocol therapy.

1.2 Secondary

- Evaluate duration of response for patients who achieve CR or PR
- Assess the duration of overall survival (OS)
- Assess progression-free survival (PFS)
- Safety

1.3 Exploratory

- Assess biologic markers including transcriptional interactomes and master regulators that may predict efficacy or toxicity of entinostat

2. BACKGROUND AND RATIONALE

2.1 Background

2.1.1 Neuroendocrine Tumors

Neuroendocrine tumors (NETs) are derived from neuroendocrine cells that reside widely in the endocrine system and other organs and comprise a heterogeneous group of neoplasms. Because NETs can arise in a broad spectrum of locations they are associated with a broad range of symptoms that may be caused by mass effects and/or by the production of hormones or biogenic amines (1,2). The diagnosis of NETs has become more common over the past three decades (3,4). The Surveillance, Epidemiology and End Result registry (SEER) has reported that NET incidence in the USA has increased from one to five per 100,000 individuals between 1973 and 2004 (2,3,5,6). Because many patients survive for prolonged periods of time the prevalence of NETs was much higher than the incidence, reaching 35 in 100,000 by 2004 (6). The most common site of malignant NETs is in the GI tract where approximately 70% of these neoplasms are found (7). Gastroenteropancreatic neuroendocrine tumors (GEP-NETs)

represent a diverse and heterogeneous set of malignancies, primarily comprising gastric (GNET), small intestine (SI-NET), rectal (RNETs), colon NETs (CNETs) and pancreatic NETs (PNETs). These tumors originate from ubiquitous neuroendocrine (NE) cells and, depending on cell of origin, have been classified into several subtypes, exhibiting distinct clinical behavior and requiring different management strategies for diagnosis and treatment (2,8).

2.1.2 Epigenetics and cancer

Epigenetics is a heritable process that alters gene expression without changing the DNA sequence (Jones 2007). This process includes DNA and chromatin modifications by methylation, acetylation, phosphorylation, ubiquitination, and sumoylation. Epigenetic modulation of gene expression occurs naturally and is essential to many organism functions, but if it occurs improperly, adverse effects ensue. The best known epigenetic process is DNA methylation, which involves the addition of a methyl group (CH_3) at the 5´ position of the pyrimidine ring of the cytosine in cytosine-guanine (CpG) islands (Issa 2007). The presence of 5'-mC in the promoter region of specific genes alters the binding of transcriptional factors and other protein modulators to DNA causing gene silencing.

Another significant epigenetic process is the post-translational modification of histones. In chromatin, histones and DNA are tightly bundled together to fit into the nucleus. This complex can be modified by histone acetylation, which alters chromatin structure to influence gene expression (Glozak 2007). In general, tightly folded chromatin tends to be silent, or not expressed, while more open chromatin is functional, or expressed. Among all the epigenetic research in cancer conducted so far, ample evidence has linked epigenetic modulation with malignant transformation and progression (Jones 2007, Baylin 2005).

2.1.3 Histone deacetylases (HDACs) and HDAC inhibitors (HDACi)

Post-translational modification of histone plays an important role in regulating gene expression. It is mediated by a variety of enzymes, including histone acetyltransferases (HATs) and histone deacetylases (HDACs) (Glozak 2007). These enzymes acetylate and deacetylate the lysine amino acid residues on histone tails. In general, histone H3 and H4 acetylation is associated with open chromatin status favoring gene expression, whereas histone deacetylation is associated with closed chromatin structure favoring gene silencing. The balance between HATs and HDACs is critical for regulating the expression of a variety of genes that are involved in cell

proliferation, survival, angiogenesis, and immunity (Heider 2006, Wang 2006, Brogdon 2007). To date, 18 HDACs have been identified in humans (Bolden 2006, Minucci 2006). They are grouped in two major categories: zinc-dependent HDACs and NAD-dependent HDACs. Furthermore, HDACs are classified into four major classes: Class I includes HDAC 1, 2, 3, 8, and 11; Class II includes HDAC 4, 5, 6, 7, 9, and 10; Class III includes SIRT 1-7, and Class IV currently includes only HDAC 11. Class III is NAD-dependent, whereas classes I, II, and IV are zinc dependent. In addition to histones, HATs and HDACs mediate post-translational acetylation on lysine residues in a variety of nonhistone proteins, including transcription factors (p53, STAT3, MYC, GATA-1, GATA-2, E2F, NF-κB, nuclear receptors, HIF-1α, and TEL), α-tubulin, and heat shock protein-90 (HSP90) (Glozak 2007, Glozak 2005).

Because HDACs target histones and a variety of nonhistone proteins that control cell survival, proliferation, angiogenesis, and immunity, they became attractive targets for cancer therapy. At the present time, the HDACi vorinostat (Zolinza, SAHA), romidepsin (Istodax®), panobinosat (Farydak®), and belinostat (Beleodaq®) have already been approved by the FDA for the treatment of patients with relapsed cutaneous T-cell lymphoma, peripheral T-cell lymphoma and / or multiple myeloma.

2.2 Entinostat (SNDX-275)

Entinostat (also known as MS-275, SNDX-275) is an orally available synthetic pyridylcarbamate licensed from Bayer Schering AG by Syndax Pharmaceuticals. Entinostat inhibits histone deacetylases (HDACs) and promotes hyperacetylation of nucleosomal histones as well multiple protein substrates.. Altered activity of HDACs and inactivation of histone acetyltransferases are key events within transformed cells. There is evidence that HDACs are associated with a wide range of solid tumors including melanomas, neuroblastomas, lymphomas, and lung, breast, prostate, ovarian, bladder, and colon cancers. In a number of *in vitro* models, HDAC inhibitors triggered growth arrest and induced cell differentiation or apoptosis. (Hess-Stumpp 2007).

Entinostat has been shown to specifically inhibit class 1 HDAC enzymes (HDAC1, 2 and 3) *in vitro* with high affinity, with an IC_{50} of 0.119 µM for HDAC1, 0.123 µM for HDAC2, and 0.181 µM for HDAC3. Indicative of its selectivity, the IC_{50} for most other HDAC isoforms was greater than 10 µM and greater than 100 µM for HDAC6. Inhibition of HDAC11 was observed at 0.427 µM, which may be relevant to entinostat's activity in Hodgkin's lymphoma (Buglio 2011).

In tumor cell cultures, exposure to entinostat at concentrations of 0.3 μM and 1 μM resulted in the accumulation of hyperacetylated histones. The levels of histone acetylation were almost identical in the different cell lines (K562, HL-60, A2780, KB-3-1, and HCT-15). Entinostat demonstrated antiproliferative activity against various human tumor cell lines including ovarian, lung, gastric, colorectal, oral, and pancreatic cancers, with IC_{50} values ranging from 0.0415 μM to 4.71 μM (Saito 1999).The antitumor effect of entinostat *in vivo* was evaluated in a wide spectrum of xenograft models, including melanoma, prostate, breast, NSCLC, pancreas, colon, ovarian, gastric, head and neck, and glioblastoma (Hess-Stumpp 2005, Hess-Stumpp 2004a, Hess-Stumpp 2004b, Hess-Stumpp 2003). Entinostat showed a dose-dependent tumor-inhibitory effect in most of the models studied. The MTD in these animal experiments under the conditions as described above was 50 mg/kg. The most prominent tumor-inhibition was found in models of melanoma, NSCLC, prostate, and breast carcinoma.

Entinostat has also been shown to modify the phenotype of cancer cells from a mesenchymal to an epithelial one, with impact on reducing the metastatic potential of the cancer cells (Shah 2014). In addition, there is a suggestion that entinostat may have longer term effects on cancer phenotypes, cancer stem cells (CSCs) or progenitor cell pool and potential sensitization to subsequent post-study treatments (Juergens 2011).

Most recently, entinostat has been shown to down-regulate the number and function of two key immunosuppressive cells, myeloid derived suppressor cells (MDSCs) and regulatory T-cells (Tregs), in the tumor microenvironment thereby enhancing the activity of immune checkpoint inhibition.

To date, entinostat has been investigated alone or in combination in >900 patients with cancer in clinical studies, including >600 patients with solid tumors. Entinostat as a single agent has been studied in metastatic melanoma and in combination has been studied in metastatic NSCLC, breast cancer, renal cell cancer, and colon cancer. Evidence of the efficacy of entinostat was seen in patients with nonresectable Stage IV melanoma, with 25% of patients experiencing disease stabilization (Hauschild 2008). Based on these encouraging findings, further investigation of entinostat in combination was considered warranted in patients with melanoma. In combination studies, clinical activity of entinostat combined with exemestane was demonstrated in ER+ post-menopausal women with advanced breast cancer enrolled in the ENCORE 301 study. Prolonged PFS and OS were observed, resulting in a breakthrough therapy designation for entinostat. A phase III study has been initiated based on the results of ENCORE 301 and is currently enrolling patients.

Overall, among all patients treated, entinostat has been well tolerated at the doses and schedules investigated. Regardless of indication and regimen, the most frequently reported adverse events (AEs) with entinostat included gastrointestinal (GI) disturbances, primarily nausea with or without vomiting and diarrhea; fatigue; and hematologic abnormalities, primarily anemia, thrombocytopenia, neutropenia, and leukopenia. Most occurrences of these events are Grade 1 or 2 in severity and non-serious. Grade 3 and 4 hematologic abnormalities are commonly seen in patients with hematologic malignancies, but are much less prevalent in patients with solid tumors.

Additional information on the chemistry, pharmacology, toxicology, preclinical findings, and clinical experience to date may be found in the Entinostat Investigator's Brochure.

2.3 STUDY RATIONALE

2.3.1 Master regulators in NET cells that predict HDACi sensitivity

Identification of small molecule compounds targeting NET vulnerabilities proceeded along two distinct steps.

First master regulator (MR) proteins representing key functional dependencies of metastatic progression were identified, on an individual sample basis, using the Master Regulator Inference algorithm (MARINa) (Carro 2010, Aytes 2014). Then patient-derived GEP-NET samples presenting the highest MR overlap (≥ 75%) with those of available hepatic metastases cell lines (H-STS) were selected. These represent ~10% of the total metastatic GEP-NET cohort across colorectal, small-bowel, and pancreatic NETs. shRNA-mediated validation of the top 30 positive MRs from these patients in H-STS cell lines showed that >50% of these proteins are essential for tumor cell viability.

Second, 118 compounds were pre-selected in collaboration with the Broad Institute based on their differential activity in GEP-NET cells (KRJ-I, H-STS, P-STS, and L-STS) vs ~350 other pan-cancer cell lines in the cancer cell line encyclopedia (CCLE) (Basu et al. 2013 Cell **154**(5): 1151-1161). These compounds were then prioritized based on their ability to inhibit and activate the top 25 positive and negative patient specific MR proteins, respectively. This was accomplished by performing RNAseq profiling of H-STS cells following compound perturbation at two concentrations (the 48h IC_{20} and 1/10 of that concentration) and at two time points (6h and 24h).

Protein activity following compound perturbation was assessed using the MARINa algorithm. Entinostat emerged as the most potent compound as well as the one presenting the strongest sustained effect at 24h at both concentrations.

2.3.2 Entinostat (SNDX-275) induces *in vivo* inhibition of HST-S cells

We validated three compounds in H-STS xenograft models in collaboration both with Champions Oncology and with the Andrew Kung's lab at Columbia. These compounds included entinostat, tivantinib, and belinostat, predicted to have high, low, and negligible potency respectively in reverting activity of patient specific MR proteins. Assays from both labs confirmed that entinostat produced significant tumor size reduction over 25 days, while tivantinib had only a modest effect (40% viability reduction compared to DMSO, as predicted) and belinostat was indistinguishable from DMSO treated controls, also as predicted. Consistent with the analysis, entinostat activity was virtually identical at two different doses. From this analysis, considering that activity of the drugs was prioritized purely based on patient derived data and that cell line assays were used strictly to assess compound mechanism of action, in term of targeting critical MR proteins, we estimate that a minimum of 10% of GEP-NET patients should be highly sensitive to entinostat.

2.4 Dose Selection

Entinostat has been evaluated *in vitro*, in nonclinical *in vivo* studies, and in Phase I and II studies in patients with various solid tumors and hematological malignancies at doses between 2 and 12 mg/m^2 and at dosing frequencies ranging from once daily to every 2 weeks. Increased histone acetylation was observed at the lowest dose evaluated with the effect persisting at least 48 hours post-dose. PK studies of entinostat have indicated a long half-life of entinostat, ranging from 40 hours to 120 hours. Consistent with this long half-life, entinostat concentrations were detectable 168 hours post-dose at doses of 2 to 12 mg/m^2.

The maximum tolerated dose (MTD) for single agent entinostat in non-hematologic indications was established as 4 mg/m^2 weekly × 3 and 1 week rest, or 10 mg/m^2 every other week continuously.

Pharmacokinetic analyses have demonstrated ~40% variability in the clearance of entinostat. However, when clearance was adjusted for body surface area (BSA), the inter-patient variability was similar. A linear regression analysis on factors that may contribute to this variability, such as ideal body weight, lean body mass, body weight, and body mass index, were not significant

covariates. As a result of this analysis, fixed dosing is considered to be as accurate as dosing based on BSA (Alao 2004). Entinostat given once weekly continuously at a dose of 5 mg (in combination with the aromatase inhibitor exemestane) in a clinical study in patients with locally advanced or metastatic breast cancer and given every other week continuously at a dose of 10 mg (in combination with erlotinib) in patients with stage IIIB/IV NSCLC was well tolerated. Entinostat's AE profile at these dose schedules was consistent with previous clinical experience, with the most common AEs being fatigue and gastrointestinal disturbances, (nausea, vomiting, and diarrhea).

2.5 Scientific Hypothesis

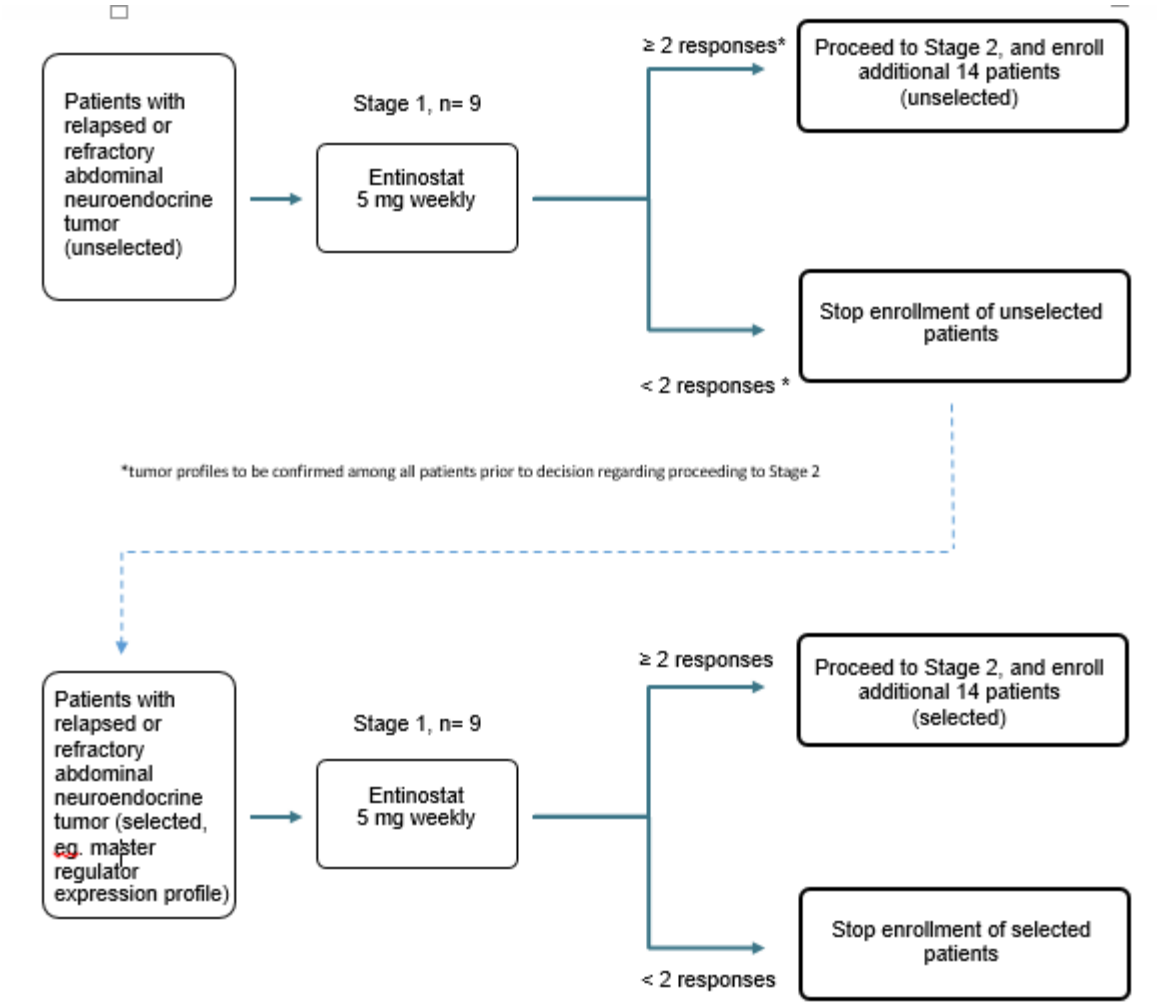
It is hypothesized that entinostat will:

- inhibit proliferation of a subset of abdominal neuroendocrine tumors with a signature transcriptional interactome
- arrest tumor progression as evidenced by tumor shrinkage or stabilization in the study patient population.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is an open-label, single arm, multi-center Phase II trial of entinostat given as a 5 mg oral dose every week (days 1, 8, 15, and 22 of a 4-week cycle) in patients with relapsed or refractory abdominal neuroendocrine tumors. Patients will continue on treatment until disease progression or intolerable toxicity occurs.



3.2 Number of Centers

Up to 4 study centers in the US will be recruited for participation in the study.

3.3 Number of Patients

Up to 40 patients with relapsed or refractory abdominal neuroendocrine tumors may be enrolled to achieve up to 32 response-evaluable patients. Safety will be evaluated in an ongoing fashion. It is anticipated that no more than 25% of enrolled patients will be non-evaluable for response.

4. PATIENT ELIGIBILITY

4.1 Inclusion Criteria

Patients must fulfill all of the following inclusion criteria in order to be admitted into the study:

1. Pathologically confirmed stage IV unresectable relapsed, or unresectable refractory abdominal neuroendocrine tumor from the last biopsy available which may be the initial diagnostic biopsy.
   Relapsed disease is defined as progressive disease following systematic therapy with lanreotide or equivalent. Refractory disease is defined as disease not responding to or having progressed within 1 month of the last dose of most recent systemic therapy to include lanreotide or an analog. (Note, small cell carcinoma and large cell undifferentiated neuroendocrine tumors will be excluded from this trial).
2. Eligibility for stage 2 of the study, if the extension stage is opened, will be determined by RNAseq analysis and master regulator profile of a single fresh needle biopsy specimen obtained during study screening.
3. Documented disease that is radiographically measurable.
4. Last dose of prior therapy must be > 14 days before the first dose of study drug administration. There is no upper limit to number of prior therapies. However, the patient must have recovered from acute toxicities from the most recent therapy to grade 1 or less.
5. ECOG performance status of 0 or 1 (must be done within 7 days prior to study drug administration).
6. Age 18 years or older
7. Total Bilirubin $\leq$ 1.5 x Upper Limit of Normal (ULN) and AST and ALT $\leq$ 2.5 x ULN (results within 7 days before study drug administration), ≤5×ULN for patients with liver metastases.
8. Serum creatinine $\leq$ 1.5 x ULN (results within 7 days before study drug administration)
9. Absolute neutrophil counts of $\geq$ 1500/μL (without growth factor support), platelet counts $\geq$100,000/μL (without transfusion support); and hemoglobin ≥9 g/dL results within 7 days before study drug administration.
10. Patients or their legal representative must be able to read, understand, and sign a written informed consent
11. International Normalized Ratio (INR) or Prothrombin Time (PT) ≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants AND Activated Partial Thromboplastin Time (aPTT) ≤1.5×ULN unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
12. If a female of childbearing potential, has a negative serum blood pregnancy test during screening and a negative urine pregnancy test within 3 days prior to receiving the first dose of study drug. If the screening serum test is done within 3 days prior to receiving the first dose of study drug, a urine test is not required. Note: Women of childbearing potential (WoCP) are any women between menarche and menopause who have not been permanently or surgically sterilized and are capable of procreation. Permanent sterilization includes hysterectomy and/or bilateral oophorectomy and/or bilateral salpingectomy but excludes bilateral tubal occlusion. WoCP include non-women who have experienced menopause onset < 12 months prior to enrollment.
13. If a female of childbearing potential, willing to use 2 methods of birth control or willing to abstain from heterosexual activity for the course of the study through 120 days after the last dose of study drug.
14. If male, agrees to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of study drug.

4.2 Exclusion Criteria

Patients fulfilling any of the following criteria will not be admitted into the study:

1. Patients with another active cancer (excluding basal cell carcinoma or cervical intraepithelial neoplasia [CIN / cervical carcinoma in situ] or melanoma in situ). Prior history of other cancer is allowed, as long as there is no active disease within the prior 5 years.
2. Pregnant or lactating women. Women of child-bearing potential (WOCBP) must have a negative serum pregnancy test documented within 3 days prior to start of study drug.
3. Patients with uncontrolled intercurrent illness, active or uncontrolled infections, or a fever >38.5°C that has not been evaluated for infection up to the day of initial dosing. Patients with documented history of tumor fever are accepted provided acute or chronic infection has been excluded as possible cause of the fever.
4. Patients who have been treated with any investigational drug within 28 days prior to the first dose of study medication, or who are receiving concurrent treatment with other experimental drugs or anti-cancer therapy.
5. Prior treatment with HDAC inhibitors (e.g. valproic acid, Zolinza® (SAHA), romidepsin (Istodax®).
6. History of pericarditis or pericardial effusion that had required medical or surgical intervention in the last 6 months, or myocardial infarction or arterial thromboembolic events within 6 months, or experiencing severe or unstable angina, or New York Heart Association (NYHA) Class III or IV disease, or a QTc interval >0.47 seconds
7. Known HIV or a history of active Hepatitis B or C as evidenced by laboratory abnormalities in addition to positive serology. Testing is not required for patients not suspected of having these conditions
8. Any condition (e.g., known or suspected poor compliance, psychological instability, geographical location, etc) that, in the judgment of the investigator, may affect the patient's ability to sign the informed consent and comply with study procedures
9. Any condition that will put the patient at undue risk or discomfort as a result of adherence to study procedures
10. Presence or history of brain metastases.
11. Uncontrolled hypertension or diabetes mellitus
12. Any contraindication to oral agents or significant nausea and vomiting, malabsorption, or significant small bowel resection that, in the opinion of the investigator, would preclude adequate absorption.
13. Allergy to benzamide or inactive components of entinostat.
14. Patients may not be taking any corticosteroid for any reason while on study and all corticosteroids must be stopped two weeks prior to initiation of study drug.

5. PATIENT ENROLLMENT

All patients will be screened by the study site's principal investigator or one of the study site's sub-investigators prior to entry on this study. An explanation of the study and discussion of the potential risks and benefits will be fully disclosed to the patients prior to the screening process in

order for the patient to provide a voluntary written informed consent. Only eligible and consenting patients will be entered into the study.

The screening period for a patient commences when the patient signs the informed consent form. The consent form must be signed before any study-specific tests are performed.

The IRB / EC of an institution must approve the consent form document to be used at the center prior to its local activation; changes to the consent form during the course of the study will also require IRB / EC notification/approval.

Patients who cannot give informed consent (i.e. mentally incompetent patients, or those physically incapacitated such as comatose patients) are not to be recruited into the study. Patients competent but physically unable to sign the consent form may have the document signed by their legal guardian. Each patient will be provided with a full explanation of the study before consent is requested.

All participants must be centrally registered through the Central Registration Office within Herbert Irving Comprehensive Cancer Center at CUMC prior to initiation of study treatment.

Registration hours are available Monday through Friday from 9:00am – 5:00pm EST (excluding holidays and weekends). Same day patient registrations (and after hour registrations) will be accommodated on a case by case basis provided that the study team has expressed all time sensitive registration concerns/cases in a timely manner to the Central Registration Office.

CPDM Central Registration Procedures:

Within 48 hours of obtaining consent (excluding holidays and weekends), a completed/signed IRB approved informed consent HIPAA form, and demographics forms must be submitted to the CPDM Central Registration Office via an email to CPDMRegistration@columbia.edu or fax to 212.305.5292, with the subject line "AAAR1117 Pending Subject Registration Request (PHI)". Upon receipt, applicable subject information as well as a "pending eligibility" status will be entered into HICCC's institutional database. This status will remain until further source documentation is made available to confirm overall patient eligibility. Required materials for all pending registration submissions are as follows:

- Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable.
- The completed/signed IRB approved HIPAA Authorization form
- Completed/signed CPDM ICF checklist
- Completed/signed HICCC personal census form
- Completed/signed CPDM Demographics Note to File

In order to confirm eligibility status, Investigators/designees (e.g., study specific Clinical Research Coordinator/Research Nurse, etc.) must submit the following documentation to the Central Registration Office via email or fax:

- The completed/signed study specific Eligibility Checklist (signed by an Physician level Investigator)
- Copies of source documentation necessary for each item to be verified on the CPDM specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) or other appropriate medical records capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
    - Protocol deviation/waiver approvals (if applicable)
- **Please note**: subject line of email or fax should include the following: "AAAR1117 Complete Subject Registration Request (PHI)".

Upon receipt of the above mentioned documentation, participant eligibility information will be verified by a qualified Central Registration Registrar. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable study team personnel for clarification prior to enrollment. .All applicable finalized registration/eligibility information will then be entered into HICCC's institutional CTMS database by the Central Registration Registrar.

Upon completion, an official subject registration notification email will be sent to the PI/research team which will include eligibility/enrollment status, as well as subject ID information. Protocol therapy may not be initiated prior to receipt of this notification from the Central Registration Office.

All screen fail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

6. TREATMENT PROCEDURES

The responsibility for treatment of patients rests with the individual Investigator. The protocol treatment is to begin within 14 days of the screening visit.

6.1 Entinostat Administration

The starting dose of entinostat will be 5 mg administered orally every week (days 1, 8, 15, and 22) of a 28 day treatment cycle. The dose may be changed from 5 mg weekly to 10 mg every two weeks after cycle 1 for patients who have not experienced treatment-related adverse events (excluding manageable events) with severity grade ≥2 (moderate). Provisions for dose reductions are described in Section 6.3.

Entinostat is supplied in 5 mg (intense yellow in color) and 1 mg (light brown in color) coated tablets. Study drug should be taken in the morning. Tablets should be taken on an empty stomach, at least 2 hours after a meal and at least 1 hour before the next meal.

Tablets should be taken whole and not crushed. If a patient vomits after taking a dose of medication, dosing should not be re-administered but instead the dose should be skipped. If the patient inadvertently missed the dose on scheduled day, the dose could be taken within 2 days of the scheduled dose. However, all efforts should be made to adhere to dosing schedule.

Procedures for dose reductions and delays due to toxicity are summarized in Section 6.3. In the event of necessary dose reductions, each study site pharmacy will be supplied with 1.0 mg tablets in addition to the 5.0 mg tablets.

Unused tablets or empty bottles will be returned to the clinic for accountability purposes.

6.2 Treatment Duration

Patients who display progressive disease or unacceptable toxicity to treatment will be removed from protocol treatment at the time that event is documented. Further disease management will be at the investigator's discretion. If the patient withdraws from study treatment due to toxicity related to study drug, the patient will be followed until the resolution or conclusion of the event.

All patients will be treated until progression or intolerable toxicities occur.

6.3 Dose Adjustments

Adverse events that are classified as unrelated or unlikely related do not require dose adjustment, and the prior dose can be resumed once the adverse event has resolved. For toxicities that are classified as possibly related to the AE, dose adjustment should be addressed as follows:

For patients who are escalated to 10 mg every two weeks, any toxicity ≥ Grade 2 will result in an initial reduction to 5 mg every two weeks. If the grade of the toxicity is ≤ grade 2 for all toxicities or ≤ grade 3 for laboratory abnormalities other than hepatic, renal or hematologic, an increase in dose to the prior level can then occur after the toxicity has completely resolved and the 5 mg every two weeks dose has been shown to be tolerable. Patient may then receive either 10 mg every two weeks or 5 mg every weekat the discretion of the investigator.

6.3.1 Entinostat-Related Non Hematologic Toxicity

The rules outlined in Table 6-1 are to be followed for the management of non-hematologic toxicities that are probably or definitely due to entinostat, with toxicities graded by the Investigator according to the NCI, CTCAE, version 4.03.

Table 6-1 Non-hematologic Toxicity: Dose Modifications for Entinostat

Toxicity	Dose modifications[1]
Grade 4	Administer symptomatic remedies/ start prophylaxis. Hold dose until recovery to Grade 1 or baseline under the following directions. 1. If recovered within 4 weeks of onset (i.e.: ≤3 missed doses) , resume study drug as follows: • If receiving 10 mg bi-weekly, restart study drug at 5 mg weekly. • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg • If receiving 2 mg, discontinue study treatment 2. If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Grade 3	Administer symptomatic remedies/ start prophylaxis. Hold dose until recovery to Grade 1 or baseline under the following directions: 1. If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose or per investigator's discretion. 2. If not recovered by either of the next 2 scheduled doses and receiving 2 mg, permanently discontinue study treatment. Otherwise, skip each dose and if recovered by the 4th dose, resume study drug as follows: • If receiving 10 mg bi-weekly, restart study drug at 5 mg weekly. • If receiving 5 mg, restart study drug at 3 mg. • If receiving 3 mg, restart study drug at 2 mg. 3. If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Recurrence of the **same** Grade 3 toxicity despite dose reduction	If the **same** ≥Grade 3 event **recurs:** 1. Administer symptomatic remedies/ start prophylaxis. If receiving 2 mg, permanently discontinue study drug. Otherwise, hold[1] dose until recovery to Grade 1 or baseline. 2. If recovered for either of the next 2 scheduled doses, resume study drug as follows: • If receiving 10 mg bi-weekly, restart study drug at 5 mg weekly. • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg 3. If the **same** ≥Grade 3 event **recurs** (i.e., third occurrence) despite entinostat dose reduction to 2 mg, as described above, discontinue study drug.
≤Grade 2	Administer symptomatic remedies / start prophylaxis. Dosing of study drug may be interrupted at the Investigator's discretion, in consultation with the Medical Monitor. • If dose is held for 4 consecutive weeks, permanently discontinue study drug.[2] • If toxicity resolves, resume entinostat at the original dose.

[1] *If Entinostat dose is reduced, an increase in dose to prior level can occur only after the AE has completely resolved.*

[2] *If greater than 50% of doses are missed during any 6 week period, discontinue from study drug treatment.*

Please note: *Patients that do not require a dose reduction due to AE during the first treatment cycle should continue at 5mg weekly for at least one more cycle prior to changing to 10mg biweekly.*

6.3.2 Entinostat-related Hematologic Toxicity

The guidelines in Table 6-2 will be followed for determining the timing of cycles based on hematologic status at the time of planned dosing.

Table 6-2 Hematologic Toxicity: Dose Modification for Entinostat

Toxicity	Dose modifications[1]
≥Grade 3 neutropenia, ≥Grade 3 uncomplicated thrombocytopenia, or Grade 2 complicated thrombocytopenia	Administer symptomatic remedies/ start prophylaxis. Hold dose[2] until recovery to Grade 1 or study baseline. 1. If not recovered by next scheduled dose, skip the dose. If recovered by next scheduled dose, resume study drug at prior dose. 2. If receiving 2 mg dose, and not recovered by either of the next 2 scheduled doses, permanently discontinue study treatment. Otherwise, skip each dose. If recovered for either of these doses, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg. • If receiving 3 mg, restart study drug at 2 mg. 3. If dose is held for 4 consecutive weeks, permanently discontinue study drug.
Recurrence of the **same** hematologic toxicity	If the same hematologic toxicity **recurs**: 1. Administer symptomatic remedies/ start prophylaxis. If receiving 2 mg, permanently discontinue study drug. Otherwise, hold dose until recovery to Grade 1 or baseline. 2. If receiving 2 mg dose, and not recovered by either of the next 2 scheduled doses, permanently discontinue study treatment. If recovered for either of the next 2 scheduled doses, resume study drug as follows: • If receiving 5 mg, restart study drug at 3 mg • If receiving 3 mg, restart study drug at 2 mg 3. If the **same** ≥Grade 3 event **recurs** (i.e., third occurrence) despite entinostat dose reduction to 2 mg, as described above, discontinue study drug.

[1] *If Entinostat dose is reduced*, *an increase in dose to prior level* can occur only after the AE has *completely resolved.*

[2] *If greater than 50% of doses are missed during any 6 week period, discontinue from study drug treatment.*

Please note: *Patients that do not require a dose reduction due to AE during the first treatment cycle should continue at 5mg weekly for at least one more cycle prior to changing to 10mg biweekly.*

6.4 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive and palliative care with the exception of those listed in Section 6.5. Please note: Patients on somatostatin analogues for symptom control may continue to receive them for symptom control.

6.5 Prohibited Medication

The following medications are prohibited:

- Valproic acid, Zolinza™ (vorinostat), Istodax® (romidepsin) or any other HDAC inhibitor
- DNA methyltransferase inhibitors (such as azacytidine (Vidaza®), decitabine (Dacogen®), and any experimental DNA methyltransferase inhibitor compounds),
- Other anticancer treatment including, but not limited to chemotherapy and radiotherapy.
- Corticosteroids. Topical steroids, such as nasal sprays, inhalers, ointments, are allowed. Systemic glucocorticoids are allowed for emergent medical conditions such as seasonal allergies and exacerbation of COPD for up to 2 continuous weeks; the medical monitor must be notified if such drugs are initiated for emergent conditions and be consulted should prolonged treatment be required. In patients with severe nausea or vomiting refractory to available anti-emetic therapies other than corticosteroid, a single dose of dexamethasone up to 10 mg (or equivalent), as part of antiemetic regimen to treat or prevent emesis is allowed. Patients should not have received corticosteroids for treatment of any disease within 2 weeks of Cycle 1 Day 1.
- Other investigational therapy
- Radiation therapy

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case-by-case basis after consultation with sponsor. The patient must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression.
- Traditional herbal medicines; these therapies are not fully studied and their use may result in unanticipated drug-drug interactions that may cause or confound the assessment of toxicity

6.6 Medications to Avoid

The following types of medications should be avoided if possible:

- Gastric acid reducing drugs (e.g. proton pump inhibitors [PPI], histamine receptor antagonists [H2], antacids; see Appendix 3)
- Sensitive substrates of CYP1A2, CYP2C6, and CYP2B8 (see Appendix 3)
- Drugs that are known to inhibit or induce P-gp (see Appendix 3)

7. STUDY TESTS AND OBSERVATIONS

Protocol-required tests, observations, and procedures are summarized in the Schedule of Study Assessments. Each cycle consists of 28 days. Patients will self-administer entinostat as described in Section 6.1. During cycle 1, patients will be required to visit the clinic on Days 1, 8, and 15. For all other cycles, patients will be required to visit the clinic on Day 1 and 15 only.

7.1 Screening

Screening tests are to be performed within 14 days prior to Cycle 1 Day 1 (C1D1) except as otherwise indicated.

- Informed Consent
- Medical history, including current medications taken within the past 28 days
- Physical examination
- Vital signs and weight
- ECOG performance score
- 12-lead ECG (within 14 days prior to C1D1)
- Coagulation tests (PT, PTT)
- Serum pregnancy test for women of child bearing potential only
- Hematology (CBC with differential, PLT, RBC, HGB, HCT)
- Blood chemistries [ALT, AST, alkaline phosphatase, albumin, total bilirubin, BUN, calcium, creatinine, electrolytes (sodium, potassium, magnesium, chloride, bicarbonate), glucose, LDH, phosphorus, total protein], uric acid.
- Urinalysis
- Contrast CT **and** octreotide scan for disease assessment (if one has not been performed within 28 days prior to C1 D1). The same method used at baseline should be used for all serial measurements.

- Clinical disease assessment for palpable or visual lesions
- Assessment of baseline signs and symptoms (adverse events will be collected starting at the time the patient signs the informed consent form and will be listed as pre-treatment emergent)
- Access to archival pathology tissue is required for molecular analysis. If archival tissue is not available for molecular analysis, tumor biopsy may be requested if there is a metastatic site easily accessible for needle biopsy.
- Concomitant medications taken within 28 days of cycle 1 day 1

7.2 Day 1 Visit Assessments (All cycles)

Patients will make clinic visits for tests and observations according to the schedule in Schedule of Study Assessments (Appendix 1). Assessments may be performed up to 2 days and CT/ scans may be performed up to 7 days prior to the scheduled study visit day. The results of study blood tests must be available and reviewed by study site staff for toxicity and adverse events before the next dose of entinostat is administered. Obtaining blood for these tests may be performed locally or drawn by a home health care worker if clinic visits are not practical. Results must be sent to the investigator. Other observations should be performed prior to the next dose of entinostat.

Required procedures are as follows:

- Concomitant medications
- Adverse Events
- Hematology (as at screening)
- Blood chemistries (as at screening with the exception of magnesium which does not need to be done unless clinically indicated)
- Symptom directed PE (capture B symptoms)
- Vital signs and weight
- ECOG performance score
- Clinical disease assessment for palpable or visual lesions
- CT scan for disease assessment (up to 7 days prior to day 1 of odd cycles beginning with Cycle 3). In patients completing >9 cycles, scans are required every 3-4 months and/or omitting the use of contrast dye to every other restaging. Follow-up scans should include

the area of interest, the prospectively selected indicator lesion(s); the same method used at baseline should be used for all serial measurements.

- Entinostat compliance assessment

7.3 Day 8, 15, 22 Visit Assessments

See Appendix 1 for full details on required visit assessments for Day 8, 15, and 22 visits according to cycle number.

7.4 End of Treatment Visit Assessments

This visit should occur within one week from the date that the physician decides to discontinue study treatment. If the physician decides to discontinue study treatment due to disease progression, this visit should be completed before beginning the patient on another therapy.

Required procedures are as follows:

- Physical examination
- Vital signs and weight
- ECOG performance score
- ECG (as at screening)
- Concomitant medications
- Adverse events
- Hematology (as at screening)
- Blood chemistries (as at screening with the exception of magnesium which does not need to be done unless clinically indicated)
- Contrast CT scans for disease assessment if progression has not been observed previously. Follow-up scans should include the area of interest, the prospectively selected indicator lesion(s); the same method used at baseline should be used for all serial measurements. Octreotide scans should be done if any mass detected by CT completely resolves during treatment.
- Compliance assessment
- Clinical disease assessment for palpable or visual lesions

7.5 Safety Follow-up Visit

Patients terminating study drug will return to the clinic within 30 days following the End of Treatment visit for the following procedures.

- Physical examination
- Vital signs and weight
- ECOG performance score
- 12 lead ECG (if new abnormality is observed during study and not resolved at EOT)
- Concomitant medications
- Adverse events
- Hematology (if new abnormality is observed during study and not resolved at EOT)
- Blood chemistry (if new abnormality is observed during study and not resolved at EOT)
- Any other tests required for appropriate follow-up given the nature of the toxicity

7.6 Post-study Follow-up

Once patients have progressed, they will be followed via phone call (or access via available medical records) every 3 months after disease progression for overall survival. Medical records including laboratory, pathology, operative, and radiology reports will be obtained at the discretion of the principal investigator with permission from the patient. Patients who have stopped the study drug due to toxicity should be followed until resolution of toxicity or the safety follow-up visit, whichever comes later.

8. CORRELATIVE STUDIES

Biomarker Evaluations

8.1 Tissue Sampling

A requirement of phase 2 protocol entry is the presence of a metastatic focus accessible to biopsy. All patients who enter the second phase of the trial that would require a specific gene expression profile for eligibility will be asked to undergo a single image-guided fine-needle biopsy. For patients in the first part of the protocol who agree, a minimum of 0.05mg of fresh metastatic tissue (a single needle core biopsy) will be obtained prior to treatment initiation for RNAseq and master regulator analysis. If the protocol extends to the second part, all patients

will be required to undergo biopsy in order to establish eligibility for the second part of the study if it is initiated.

9. REMOVAL OF PATIENTS

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or the institution. If a patient chooses to withdraw from study treatment, they will be asked to continue to receive follow-up via telephone. Patients have the right to withdraw completely or continue to be followed long term with telephone calls.

10. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

10.1 Adverse events

Investigational Agent: Include a comprehensive list of all reported adverse events and any potential risks (such as the toxicities seen with another agent of the same class or risks seen in animals administered this agent) as provided by the manufacturer.

Adverse Event List(s) for Other Agent(s): For each commercial agent, please provide a list of those adverse events most likely to occur on this study, and refer the reader to the package insert(s) for the comprehensive list of adverse events.

10.2 Definitions

Adverse Event:

An adverse event (AE) is any untoward or unfavorable medical occurrence in a human subject, including abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal
- is associated with a serious adverse event
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

Serious Adverse Event:

Adverse events are classified as serious or non-serious. A serious adverse event is any AE that is:

- fatal
- life-threatening
- requires inpatient hospitalization/prolongation of existing hospitalation, unless:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (procedures such as central line placements, paracentesis, pain control)
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above/below and not resulting in hospital administrations
    - social reasons and respite care in the absence of any deterioration in the patient's general condition
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

All adverse events that do not meet any of the criteria for serious events should be regarded as non-serious adverse events.

Unanticipated Problem:

An unanticipated problem is any incident, experience or outcome involving risks to subjects or others in any human subjects research that meets all of the following criteria:

- Unexpected (in terms of nature, severity or frequency) given (a) the research procedures that are described in the IRB-approval protocol and informed consent document, and (b) the characteristics of the subject population being studied;
- Related or possibly related to participation in such research (e.g., there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
- Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Adverse Event Reporting Period

The study period during which adverse events must be reported is normally defined as the period from the initiation of any study procedures (e.g., after the first dose of study treatment) to the end of the study treatment (e.g., last dose of study treatment) and/or follow-up. For this study, the study treatment follow-up is defined as 30 days following the last administration of study treatment, **or** 30 days **following the decision to remove the subject from study treatment, whichever is earliest.**

Baseline/Preexisting Condition

A baseline/preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an adverse event if the frequency, intensity, or if the character of the condition worsens during the study period.

General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of an adverse event must also be recorded and documented as an adverse event.

Post-study Adverse Event

All unresolved adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, or the adverse event is otherwise explained. At the last scheduled visit, the investigator should instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study.

Abnormal Laboratory Values

A clinical laboratory abnormality should be documented as an adverse event if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality
- The abnormality suggests a disease and/or organ toxicity
- The abnormality is of a degree that requires active management (e.g., change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.).

Hospitalization, Prolonged Hospitalization or Surgery

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event unless specifically instructed otherwise in

this protocol. Any condition responsible for surgery should be documented as an adverse event if the condition meets the criteria for an adverse event.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should **not** be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

10.3 Recording of Adverse Events

At each contact with the subject, the investigator must seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately in the source document, and also in the appropriate adverse event module of the case report form (CRF). All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All adverse events occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period must be followed up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation should be recorded and reported immediately.

10.4 Reporting of Serious Adverse Events

10.4.1 IRB Notification by Sponsor-Investigator

Reports of all events (including follow-up information) that meet the definition of an unanticipated problem posing risk to subjects or others must be submitted to the IRB within one week (5 business days) following the occurrence of the unanticipated problem or the principal investigator's acquiring knowledge of the unanticipated problem in accordance with IRB policy.

Additionally, the sponsor-investigator will submit a summary of all Unanticipated problems that occurred since the beginning of the study at the time of continuing review. Copies of each report and documentation of IRB notification and receipt will be kept in the Regulatory binder.

10.4.3 FDA Notification by Sponsor-Investigator

The Columbia University Medical Center Sponsor-Investigator, as holder of the IND, will be responsible for all communication with the FDA. Columbia University Medical Center Principal Investigator will report to the FDA, regardless of the site of occurrence, any adverse event that is serious, unexpected and there is evidence to suggest a causal relationship between the drug and the adverse event. These must be reported to the FDA and any affiliate sites as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting. The Sponsor-Investigatro will also submit an IND annual report to the FDA in accordance with 21.CFR 312.33.

The Columbia University Medical Center Sponsor Investigator must report to the FDA and any affiliate site investigators as follows:

- Any unexpected fatal or life-threatening event must be reported as soon as possible, but no later than 7 calendar days after the sponsor investigator initial receipt of the information
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any findings from animal or in vitro testing whether or not conducted under an IND, and whether or not conducted by the sponsor-investigator, that suggest a significant risk in humans exposed to the drug must be reported as soon as possible but no later than 15 calendar days after the sponsor-investigator determines that the information qualifies for reporting
- Any clinically important increase in the rate of a serious suspected adverse reactions over that listed in the protocol or Investigator Brochure
- Expected SAEs and AEs will be included in the IND Annual Reports.

Follow-up information to a safety report should be submitted as soon as the relevant information is available. However, if the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable are so reportable, the sponsor investigator must report such experience as soon as possible, but no later than 15 calendar days after the determination is made.

All other serious unexpected experiences associated with the use of the study treatment will be reported to FDA as soon as possible but in no event later than 15 calendar days after initial receipt of the information.

10.4.4 DSMC Reporting by the Sponsor Investigator

Serious adverse events not constituting unanticipated problems are to be reported to the HICCC DSMC. Reporting should occur within 24 hours of knowledge of the SAE occurring at our institution or affiliate sites.

10.4.5 Reporting to Drug Manufacturer by Sponsor-Investigator

The Sponsor-Investigator will report to investigational agent manufacturer any serious adverse events that meet the reporting criteria to the Institutional Review Board as described in section 10.4and/or to the FDA as described in section 10.4 within 24 hours/1 business day of becoming aware of it, so that these reports can be evaluated and included in the Investigator's Brochure and for IND safety submissions per regulations. Reporting will occur by sending the reporting form along with any additional documentation sent to the regulatory authorities.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Syndax tracking number and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Syndax. A copy of the fax transmission confirmation of the SAE report to Syndax should be attached to the SAE and retained with the patient records

Syndax Drug Safety Contact Information:

Email: aereporting@syndax.com
Fax: 781-419-1420

At the time of IRB renewal or at the request of the manufacturer, the Sponsor- Investigator will submit a summary of all Serious Adverse Events that have occurred inclusive of all sites to manufacturer.

10.5 Reporting Process

Adverse events may be submitted on FDA Form 3500A, the HICCC DSMC Serious Adverse Event Reporting Form, or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted above at the beginning of section 10.

11. STATISTICAL CONSIDERATIONS

11.1 Study Design

This is a Phase II, multicenter, open label, single arm study. Eligible patients will be enrolled according to Simon's two-stage design as described below. Objective response to treatment will be assessed using RECIST criteria until progression or intolerable toxicities occur, necessitating cessation of treatment.

11.2 Study Endpoints

Primary Efficacy

- Objective response rate (CR or PR) based on the patient's best response that is documented during administration of the study drug.

Secondary Efficacy

- Duration of response for patients who achieve CR or PR
- Duration of overall survival
- Duration of progression-free survival

Safety

- Incidence, severity, and duration of adverse events, including serious events and those considered by the investigator to be related to protocol therapy

11.3 Sample Size Considerations

11.3.1 Initial Protocol

Up to 40 patients may be enrolled to achieve 32 response-evaluable patients. It's anticipated that no more than 25% of enrolled patients will be non-evaluable for response.

The sample size for the expansion phase is based on a Simon 2-stage design (optimum version) and objective response rate endpoint described in Section 11.2. To calculate the required sample size, the following assumptions were made. The response probability of an ineffective therapy in this indication (i.e., the uninteresting response level) was chosen to be 15%; the response probability of an effective therapy (i.e., the targeted response level) was chosen to be at least 35%, level of significance of 10%, and power of 80%. Based on these

assumptions, the sample size of the first and second stage is 9 and 14, respectively, for a total of 23 response-evaluable patients (see below).

- If less than 2 of the 9 patients achieve an objective response (CR or PR) during the first stage of the study, enrollment will be terminated for unselected patients and entinostat will be declared to have insufficient activity in this indication in unselected patients. Thereafter, enrollment will be restricted to patients whose tumors display the characteristic master regulator expression profile consistent with hypothesized entinostat sensitivity.
- If 6 or more unselected patients achieve objective response after completion of the second stage, then entinostat will be considered sufficiently promising in this treatment setting and may be evaluated in future studies.
- If the total number of patients with objective response after completion of the second stage is between 2 and 5, further development of entinostat in this indication will be assessed. If the true objective response rate for entinostat is ≤ 15%, then the expected sample size is 14.61 patients, with probability of terminating the study at the end of the first stage equal to 60%.

Up to 40 patients may be enrolled to achieve 32 response-evaluable patients (9 unselected patients in stage 1, and 23 selected patients in stage 1 and 2).

11.4 Interim Analysis and Early Stopping Guidelines

An interim analysis is planned after enrollment in Stage 1 is complete and the primary efficacy endpoint is determined for all response-evaluable patients who are enrolled in stage 1 based on the first 6 cycles of protocol therapy. A patient is considered response-evaluable if they meet the criteria described for the per-protocol population in Section 11.5. Based on the continuation criterion described in Section 11.3, enrollment will either continue into stage 2 or will be limited to patients whose tumors display the correct master regulator profile consistent with sensitivity to entinostat.

Safety will be assessed in an ongoing fashion based on the incidence of adverse events, serious adverse events, and treatment discontinuations due to adverse event. No formal safety stopping rules are specified. However, if any significant safety issues arise, a decision to modify or terminate the trial will be made.

11.5 Planned Methods of Analysis

The full analysis set (FAS) population will include all patients who are enrolled in the study. A patient is considered enrolled in the study once the patient or legal representative grants written informed consent. The FAS population will serve as the population for a supportive analysis of the primary efficacy analysis.

The per-protocol population (evaluable patients) will serve as the population for the primary analysis of the efficacy data in this study. The per-protocol population is a subset of the FSA population and will include patients who meet all of the following criteria:

- Complete at least **two** cycles of entinostat therapy, irrespective of dose level.
- Undergo CT scans at Screening and day 1 of cycle 3.

The safety population consists of all patients who receive at least one dose of study drug. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study drug is required for inclusion in the analysis of each safety specific parameter. To assess change from baseline, a baseline measurement is also required.

12. INVESTIGATIONAL DRUG PRODUCT

12.1 Description

Entinostat is a synthetic small molecule bearing the chemical name 3-pyridylmethyl-N-{4-[(2-aminophenyl) carbonyl] benzyl}carbamate and the molecular formula $C_{21}H_{20}N_4O_3$, with a molecular weight of 376.41. Entinostat is classified as an antineoplastic agent, specifically functioning as an inhibitor of histone deacetylases, thereby promoting hyperacetylation of nucleosomal histones, allowing transcriptional activation of a distinct set of genes that leads to the inhibition of cell proliferation, induction of terminal differentiation, and/or apoptosis.

12.2 Formulation

Entinostat is orally bioavailable and is supplied as light brown or yellow coated tables containing 1.0 mg and 5.0 mg of active ingredient, respectively. Each tablet contains mannitol, carboxymethylstarch sodium, hydroxypropyl cellulose, potassium bicarbonate, and magnesium

stearate as inactive ingredients. The tablet coat contains hydroxypropyl-methyl cellulose, talc, titanium dioxide, and ferric oxide pigment as a coloring agent.

12.3 Storage and Packaging

Entinostat tablets may be shipped and stored at room temperature (20 to 25º C/68 to 77º F). Avoid temperature extremes. The pharmacist will dispense the investigational material to the patient at appropriate intervals throughout the study in childproof containers.

12.4 Drug Accountability

Unused tablets or empty bottles will be returned to the clinic to assess compliance and for entries into the case report form.

13. REGULATORY OBLIGATIONS

13.1 Informed Consent

Before a patient's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the patient or legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any investigational products are administered. The acquisition of informed consent should be documented in the patient's medical records, and the informed consent form should be countersigned by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the patient or legally acceptable representative.

13.2 Institutional Review Board (IRB)

A copy of the protocol, proposed informed consent form, other written patient information, and any proposed advertising material must be submitted to the IRB for written approval. A copy of the written approval of the protocol and informed consent form must be received by Syndax before recruitment of patients into the study and shipment of study drug.

The investigator must submit and obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document. The investigator should notify the IRB of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Syndax, in accordance with local procedures.

The investigator will be responsible for obtaining annual IRB renewals throughout the duration of the study. Copies of the investigator's submission and the IRB continuance of approval must be sent to Syndax or its representative.

13.3 Patient Confidentiality

The investigator must ensure that the patient's confidentiality is maintained. On any documents submitted to Syndax or its representative, patients should be identified only by their initials and a patient study number. Patient samples should be identified only by the patient code.

14. ADMINISTRATIVE AND LEGAL OBLIGATIONS

14.1 Protocol Amendments and Study Termination

All protocol amendments implemented by the Sponsor must receive IRB approval before implementation, except where necessary to eliminate an immediate hazard to patients. The investigator must send a copy of the approval letter from the IRB, along with the revised Informed Consent Form, to Syndax or its representative.

Both Syndax and the investigator reserve the right to terminate the study according to the study contract. The investigator should notify the IRB in writing of the study's completion or early termination and send a copy of the notification to Syndax or its representative.

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APPENDIX 1: SCHEDULE OF STUDY ASSESSMENTS

Assessments	Screening	Cycle 1				Even Cycles (2,4,6, etc.)		Odd Cycles (3,5,7, etc)		EOT	Safety F/up
		D 1 +/- 3 days	D 8 +/- 3 days	D 15 +/- 3 days	D22 +/- 3 days	D1 +/- 3 days	D15[11] +/- 3 days	D1 +/- 3 days	D15[9] +/- 3 days		
Informed consent	X										
Medical History & Medications	X[1]										
Physical exam, vitals, weight, Performance status (ECOG)	X	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X	X
Hematology and Blood chemistry tests	X[3]	X[3]		X[3]		X[3]	X[3]	X[3]	X[3]	X[3]	X
Urinalysis	X									X	
Thyroid functions: TSH, T3, T4	X									X	
Serum pregnancy test (WOCBP only)	X										
12-lead ECG	X									X	X[7]
Disease assessment / contrast CT and octreotide scan	X[4]							X[5]		X[6]	
Clinical Disease Assessment	X	X	X	X		X	X	X	X	X	
Tumor Biopsy (if archival tissue not available)	X										
Adverse events / concomitant medication information collection		X	X	X	X	X	X	X	X	X	X
Entinostat compliance assessment		X	X	X	X	X	X	X	X	X	
Entinostat drug administration		X	X	X	X	X	X	X	X		
Long Term Telephone Contact[8]											

[1]Note all medications taken within 28 days of C1D1

[2]Only a symptom directed physical exam is required at these visits.

[3]Hematology: CBC with differential, platelets, RBC, HGB, HCT; Blood chemistry: ALT, AST, alkaline phosphatase, albumin, total bilirubin, BUN, calcium, creatinine, electrolytes (sodium, potassium, magnesium {only at screening unless clinically indicated}, chloride, bicarbonate), glucose, LDH, phosphorus, total protein, uric acid.

[4]performed only if one was not done within 28 days prior to C1D1; Octreotide scan required only at screening.

[5]Follow-up scans must include the area of interest, the prospectively selected indicator lesion(s); the same method used at baseline should be used for all serial measurements. Required every 3 cycles.

[6]Performed only if disease progression was not previously documented

[7]ECG required if new abnormality is observed during study and not resolved at EOT.

[8]Following patient termination from study, every 2 months until disease progression and every 3 months after disease progression for overall survival

[9]Day 15 assessments after Cycle 1 may be performed locally or drawn by a home health care worker if a clinic visit is not practical. After 9 cycles, PE, vital signs, weight, ECOG, clinical disease assessment, hematology and chemistry are not required unless medically indicated.

APPENDIX 2: ECOG PERFOMANCE SCORE

ECOG PERFORMANCE STATUS

GRADE	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair
5	Dead

APPENDIX 3: CONCOMITANT MEDICATIONS TO AVOID

Examples of sensitive *in vivo* CYP substrates and CYP substrates with narrow therapeutic range are summarized below.

Examples of substrates that may be affected by entinostat

CYP Enzymes	Substrates with narrow therapeutic range[1]
CYP1A2	Theophylline, tizanidine
CYP2C8	Paclitaxel
CYP3A[2]	Alfentanil, astemizole[3], cisapride[3], cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine[3]

1 CYP substrates with narrow therapeutic range refers to drugs whose exposure-response relationship indicates that small increases in their exposure levels by the concomitant use of CYP inhibitors may lead to serious safety concerns (e.g., Torsades de Pointes).

2 Because a number of CYP3A substrates (e.g., darunavir, maraviroc) are also substrates of P-gp, the observed increase in exposure could be due to inhibition of both CYP3A and P-gp.

3 Withdrawn from the United States market because of safety reasons.

P-gp Inhibitors and Inducers

Inhibitors	Inducers
Amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, diltiazem, dronedarone, felodipine, lopinavir, quercetin, ranolazine, ticagrelor, ritonavir, cyclosporine, verapamil erythromycin, ketoconazole, itraconazole, quinidine	Avasimibe, carbamazepine, phenytoin, rifampin, St John's Wort, tipranavir/ritonavir

Gastric Acid Reducing Drugs

Proton Pump Inhibitors	• Omeprazole (Prilosec, Zegerid) • Lansoprazole (Prevacid) • Rabeprazole (AcipHex) • Pantoprazole (Protonix) • Esomeprazole (Nexium)
H2 Inhibitors	• Cimetidine (Tagamet) • Ranitidine (Zantac) • Famotidine (Pepcid) • Nizatidine (Axid)
Antacids	• Alka-Seltzer • Alka-2, Surpass Gum, Titralac, Tums • Milk of Magnesia • Alternagel, Amphojel • Gaviscon, Gelusil, Maalox, Mylanta, Rolaids • Pepto-Bismol

Information obtained from the following website:

Gastric acid reducing drugs: http://www.everydayhealth.com/ulcer/ulcer-treatment.aspx

APPENDIX 4: NEW YORK HEART ASSOCIATION CLASSIFICATION

The Stages of Heart Failure – NYHA Classification

Class	Patient Symptoms
Class I (Mild)	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, or dyspnea (shortness of breath).
Class II (Mild)	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, or dyspnea.
Class III (Moderate)	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, palpitation, or dyspnea.
Class IV (Severe)	Unable to carry out any physical activity without discomfort. Symptoms of cardiac insufficiency at rest. If any physical activity is undertaken, discomfort is increased.

APPENDIX 5: GUIDELINES FOR AFFILIATE INSTITUTIONS

1. Multi-site Communication:

The CPDM Office at CUMC provides administration, data management, and organizational support for the affiliate sites in the conduct of a multicenter clinical trial. The CPDM Office will coordinate, at minimum, regularly scheduled conference calls with affiliate sites.
The following issues will be discussed, as appropriate:

- Enrollment information
- Cohort updates (e.g., DLTs)
- Adverse events (e.g., new adverse events and updates on unresolved adverse events and new safety information)
- Protocol violations
- Other issues affecting the conduct of the study

2. New Protocol Distribution, IRB Submission, Modifications, and Annual Renewals

- Protocol specific documents are distributed to affiliate sites once CUMC IRB approval has been obtained.
- The affiliate site must submit a draft of site specific revisions to protocol and/or consent form documents for review and approval by the sponsor-investigator prior to submission to the local IRB. Draft documents should be sent to the study specific email address. The site will be provided confirmation that they are approved to submit to their local IRB.
- Protocol amendments must be approved by the affiliate site's local IRB within 90 days of distribution to the site by the sponsor-investigator.

3. Regulatory Documents:

Prior to Site Initiation:

Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected, prior to the initiation of an affiliate site.

- CV of PI, Co-I's and other research staff listed on FDA 1572 (signed and dated copy within 2 years)
- Medical Licenses of PI and Co-I's (current copy)
- Human subjects training certificates for PI and Co-I's
- CLIA/Laboratory Certifications for Local Laboratories listed on FDA 1572
- Local Laboratory Director's CV and License
- Local Laboratory Reference Ranges
- IRB roster or statement of compliance
- FDA Form 1572, if applicable (wet ink originals required)
- Financial Disclosure forms for all members listed on FDA 1572 (wet ink originals required)

Ongoing Regulatory Documentation: Sponsor-Investigator will ensure that proper requests are made of sites and that the following documentation is collected throughout the course of the study.

- IRB approval letters for all protocol modifications and all renewals
- IRB-approved consent forms
- Current IRB roster, if statement of compliance is not provided as part of site initiation
- FDA Form 1572, if applicable as updates are required
- Updated investigator and site information where relevant (e.g., CV, medical licensure and Financial Disclosure for new sub-investigator, local laboratory information)

Regulatory documents may be sent to R1117@columbia.edu or to the following address if wet ink originals are required:

Clinical Protocol & Data Management Office
161 Fort Washington Ave.
Herbert Irving Pavilion
Mezzanine Level, M-203
New York, NY 10032

4. Site activation

Columbia University will schedule a site initiation visit once IRB approval has been submitted from the affiliate site.

5. Central Registration Procedures- Affiliate Institution Research Participant Registration Process:

All Affiliate Institutions **must** register subjects with the coordinating center (CUMC) **prior** to any administration of study drug/intervention/local institution registration. Please see instructions below:

1. Within 48 hours of obtaining consent (excluding holidays and weekends), the Affiliate Institution CRN and/or CRC is required to submit the following documents to the coordinating center's Multicenter designee at R1117@columbia.edu. The coordinating center's designee will review the documents for accurateness, and subsequently submit the documents to the CPDM Central Registration Office via email at CPDMRegistration@columbia.edu (or via fax at 212.305.5292), with a request to register

the patient "pending eligibility." The title of the email should read, "AAR1117 Pending Subject Registration Request (PHI)". The following documents should be submitted with the pending registration request, as applicable:

a. Redacted Completed/signed IRB approved/stamped Informed Consent Forms, including additional study ICFs (e.g., tissue, DNA, etc.), as applicable
b. Redacted Signed HIPAA (or institutional equivalent)
c. MCT CPDM Velos Note to File form

2. The Affiliate Institution's investigator/research nurse/data manager/coordinator must contact the coordinating center's designee (CUMC's study specific Clinical Research Coordinator or Clinical Research Nurse) via telephone or email to communicate the following:

- Notify of pending registration request
- Confirm method of registration request submission (email or fax)
- Communicate expected time-line of registration request submission (e.g., same day, next day, within the hour, etc.)

3. To complete registration, the Affiliate Institution's investigator/research nurse/data manager/coordinator should then submit the following documents to the CUMC Multicenter designee:

- A signed Affiliate Site Eligibility Checklist (signed by the investigator)
- Copies of redacted source documentation necessary for each item to be verified on the CUMC specific Eligibility Checklist, including but not limited to:
    - Copy of required laboratory test and procedure reports (e.g., hematology, serum chemistry, pregnancy test when applicable, MRI reports, CT/bone scans, etc.)
    - Copy of pathology and surgical reports
    - Copy of clinic note(s) capturing the consent process information, along with providing source documentation of any other items needed for screening/eligibility that are not captured in other source document forms. (e.g., positive investigator statements of unique eligibility items not captured via other direct source documentation, concomitant medication lists, etc.)
    - Protocol deviation/waiver approvals (if applicable)
- **Please note**: subject line of email or fax should include the following: "AAAR1117 Complete Subject Registration Request (PHI)".

4. Upon receipt of the above mentioned documents, the designated study specific Clinical Research Coordinator will review all documents and verify patient eligibility. If any questions arise during the review process, queries in the form of emails will be addressed to the applicable affiliate site study team personnel for clarification prior to enrollment. Upon verification, the CUMC study specific designee will then forward all documents to the CPDM Central Registration Office for central registration (as described above). The CPDM Central Registration Registrar will review all applicable documents and communicate to the CUMC study specific designee in order to clarify any items. The CUMC study specific designee will communicate with the applicable site study team personnel for additional clarifications necessary prior to enrollment.

5. Upon receipt of the subject registration notification email, the CUMC study specific designee will forward the notification email (which will include the study specific patient ID)

to the affiliate site's Principal Investigator, Consenting Professional, and applicable research personnel. This notification should be filed in the patient research binder accordingly. Protocol therapy **may not** be initiated prior to receipt of this notification from the coordinating center.

6. All screenfail/ineligible subjects, as well as subject's who withdraw consent prior to enrollment/initiation of protocol therapy must be submitted to the Central Registration Office in a manner analogous to the procedures noted above. Applicable source documentation will be required within the corresponding submissions.

6. Protocol Deviation/Subject Waiver request for Affiliate Sites:

The Affiliate site MUST submit a prospective deviation request to the CUMC lead PI for review and submission to the HICCC DSMC and CUMC IRB. Approvals must be obtained from all entities prior to implementation at the Affiliate site. If a prospective protocol deviation request is submitted for review (from an Affiliate site), the PI/site memo(s), HICCC DSMC approval(s) and correspondence and CUMC IRB eligibility deviation approval letter(s) should be forwarded to the Affiliate site for documentation. The Affiliate site is also required to obtain prospective local IRB approval as per institutional policies/procedures prior to implementing the proposed deviation and registering/enrolling the subject via CUMC Central Registration. All documents and determinations must be clearly documented in the study subject's medical record, research chart and regulatory binder, as described.

7. Guidelines for Affiliate Site Monitoring

On-Site MCT Monitoring:

1. Initial, recurrent, and close-out on-site monitoring visits will also be conducted at Affiliate sites, as appropriate/feasible. Other sites will have monitoring performed remotely (see below for further details).
    a. The study Monitoring Visit Log will be completed and signed by the monitor and the PI/CRNP/CRN and/or CRC and will be filed in the regulatory binder.
2. The Compliance Coordinator will communicate with the Affiliate site coordinator/Site Principle Investigator to schedule the monitoring visit and arrange for access to study materials and documentation.
3. The Compliance Coordinator will monitor IIT trials within 1 month after the first subject is enrolled at the Affiliate site and throughout the life of the study to ensure that the study is being conducted in accordance with the protocol, GCP, applicable federal and local regulations, and per all applicable SOPs. The Compliance Coordinator is responsible to notify the participating site PI and CRNP/CRN/CRC of upcoming monitor visits and convey what information and documentation will be required for the visit(s). The Compliance Coordinator is responsible for verifying that informed consent is properly obtained, eligibility is met (via the central registration process), and all study procedures are conducted according to the study protocol. The Compliance Coordinator will also verify that the data reported in the CRF's accurately reflect source documents, that all

toxicities have been reported to date, and that all SAE's/UPs/deviations/violations have been reported according to Coordinating Center, local IRB and HICCC DSMC requirements. The Compliance Coordinator will issue queries and ensure resolution in a timely and efficient manner. The Compliance Coordinator will also monitor for applicable regulatory compliance and research pharmacy compliance (if applicable) and communicate any deficiencies as appropriate.

4. An SIV (or) teleconference will be scheduled and conducted prior to study drug being made available (if applicable) and before any subjects are enrolled on a study at the Affiliate site.

MCT Remote Monitoring:

1. When necessary (due to logistical constraints), Affiliate sites will be monitored remotely by a designated Compliance Coordinator. Sites will be informed of this remote monitoring process on a site by site basis.
2. Affiliate sites will be monitored by the Compliance Coordinator on both a regulatory level, as well as a clinical data/source documentation review level.
3. Redacted source documents (applicable to supporting the protocol specific CRF data requirements) will be sent to the designated Compliance Coordinator via fax or secure email for all subjects enrolled at Affiliate sites. Timelines for submission procedures will be defined on a case by case basis.
4. The Compliance Coordinator will review all submitted redacted source documents against the data entered on the protocol specific CRFs. The Compliance Coordinator will issue queries when/if necessary.
5. The Affiliate site research staff will respond to queries within 30 days. If queries remain outstanding, the Compliance Coordinator will send a delinquent query reminder for the outstanding items.
6. The remote monitoring procedures will include review of applicable redacted source documentation and supporting applicable documents to determine compliance regarding:
    a. Informed consent procedures
    b. Eligibility criteria
    c. Protocol specific treatment compliance
    d. Protocol specific toxicity/outcome documentation/compliance
    e. Protocol specific schedule of events (e.g., baseline visits, pre-treatment, on study, follow-up)
    f. Participating site IRB documents (e.g., IRB amendment approvals, annual renewals, SAE/UP submissions, violation/deviation submissions, INDSR submissions, etc).
    g. Required specimen submissions (e.g., tissue specimens, research blood specimens, etc.)
    h. Pharmacy accountability records
    i. Adherence to the CRF submission timeframes to CUMC (within the protocol specified timeframes)
7. Affiliate site remote monitoring reports will be sent to the lead PI, HICCC DSMC, and Affiliate sites after each remote monitoring review. Reports will include information regarding data submission timeliness/accuracy, protocol adherence items, query

resolution status, regulatory status, and overall Affiliate site performance. These reports will be generated by the Compliance Coordinator and reviewed with the Compliance Core Manager prior to dissemination.

8. Subject Randomization

Not applicable.

9. Dose Level Determinations:

The sponsor-investigator will review enrollment for each dose level cohort during the regularly scheduled conference call with the affiliate sites.
The assigned dose level for any subject to begin study treatment will be communicated to the affiliate site along with the determination by Central Registration that the subject is eligible for enrollment in the study.

10. Adverse event reporting

Sponsor reporting: Notifying participating investigators at affiliate sites of adverse events

It is the responsibility of the study sponsor to notify all affiliate sites, in a written IND safety report, of any adverse event associated with the use of the drug that is both serious and unexpected, as well as any finding from tests in laboratory animals that suggest a significant risk for human subjects. Additionally, sponsors are also required to identify in IND safety reports all previous reports concerning similar adverse events and to analyze the significance of the current event in light of the previous reports.

Serious Adverse Event Reporting

Each participating investigator is required to abide by the reporting requirements set by Columbia University Medical Center. The study must be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the principal investigator.

Participating investigators must report each serious adverse event to the Columbia University Medical Center Overall Principal Investigator within 24 hours of learning of the occurrence using the SAE Report Form. In the event that the participating investigator does not become aware of the serious adverse event **immediately** (e.g., participant sought treatment elsewhere), the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event. Report serious adverse events by telephone, email or facsimile to:

Antonio Fojo, MD PhD

Columbia University Medical Center

Herbert Irving Comprehensive Cancer Center
161 Fort Washington Avenue
New York, NY 10032
Telephone: 212-305-4604 (Multicenter Trial Number)
R1117@columbia.edu

Within the following 24-48 hours, the participating investigator must provide follow-up information on the serious adverse event. Follow-up information should describe whether the event has resolved or continues, if and how the event was treated, and whether the participant will continue or discontinue study participation.

Follow-up information is sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow- up to the previously reported SAE and giving the date of the original report. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject **continued** or withdrew from study participation or if study drug was interrupted or discontinued.

If the SAE is not previously documented in the Investigator's Brochure for the study drug (new occurrence) and is thought to be related to the investigational agent, the sponsor-investigator may urgently require further information from the investigator for reporting to Health Authorities.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported to the Columbia University Medical Center Overall Principal Investigator on the toxicity Case Report Forms.

Reporting to the Institutional Review Board (IRB) and the Data and Safety Monitoring Committee:

All Unanticipated Problems (UPs) will be reported to the CUMC IRB. SAEs not constituting UPs will reported to the HICCC DSMC.

Each affiliate site will be responsible for safety reporting to their local IRB. Investigators are responsible for complying with their local IRB's reporting requirements, though must submit the required reports to their IRB no later than 7 calendar days following the occurrence of the UP or the Principal's Investigator's acquiring knowledge of the UP. Copies of each report and documentation of IRB notification and receipt must be included in the regulatory binder.

Expected AEs must be reported at the time of continuing review of a protocol.

Guidelines for Processing IND Safety Reports

The U.S. Food and Drug Administration (FDA) regulations require sponsors of clinical studies to notify the FDA and all participating investigators of any serious and unexpected adverse experiences that are possibly related to the investigational agent. The CUMC Principal Investigator will review all applicable IND Safety Reports and has the responsibly for forwarding the IND Safety Reports to the Affiliate Institutions. The Affiliate Institution investigators are to review, send a copy to their IRB according to their local IRB's policies and procedures, and file a copy with their regulatory documents. All Affiliate site INDSR submissions, along with IRB acknowledgment (per local policies and procedures) are to be forwarded to CUMC for placement within the trial master file.

Reporting to Hospital Risk Management

Affiliate Site investigators will report to their local Risk Management Office any subject safety reports or sentinel events that require reporting according to institutional policy.

11. Confidentiality

Each affiliate site will be assigned a site number. Each subject that signs consent should be assigned a unique code number consisting of site number followed by a number with each new subject being assigned the next sequential number (e.g., 04-10). All sites will be required to enter their data in the Velos eResearch, the Clinical Trial Management System used for all Cancer-related clinical research at CUMC. All users must login with their own application username and password. Users off campus must first access the Virtual Private Network with their assigned campus username and password and then use their application credentials.

Subject confidentiality must be maintained according to HIPAA regulations and GCP recommendations.

Except when required by law, study information shared with persons and organizations outside of Columbia University Medical Center must not identify the patient by name, social security number, address, telephone number, or any other direct personal identifier.
If the results of this research project are published or presented at a scientific or medical meeting, the patient not be identified. Otherwise, all results will be kept confidential and will not be divulged (except as required by law) without permission.

12. Data Reporting Plan

Columbia University Medical Center (CUMC) is deeply committed to research integrity and strong credibility when it comes to the discovery of new treatment concepts, implementation of new clinical research techniques, and acceptance of its researcher's findings by the medical establishment. In accord with these ethics, CUMC encourages and supports its investigators in the sharing of final research data and/or details of newly developed clinical treatments.

CUMC's policies that pertain to patient data sharing conform to CUMC IRB rules, local and state laws, and HIPAA privacy regulations. The primary reason for this is to protect the privacy of patients who participate in clinical trials. The data can be made available for continuing review by federal agencies upon request and for ongoing study safety reviews by the Principal Investigator, Statistician, Data Safety and Monitoring Board (DSMC), and, in other instances, the CUMC IRB.

Data collected during the course of this clinical trial will primarily be shared with other investigators and University staff, the IRB, FDA, and other reporting agencies, and/or transferred to other collaborators. Prior to transfer, the data collected must comply with, and must be limited by, the CUMC's guidelines for Protecting the Rights and Privacy of Human Subjects.

13. Data Acquisition and Submission

Informed consent, including HIPPA authorization, must be obtained on all subjects prior to their participation. Always keep the original signed and dated consent form, with the redacted source documents and eligibility checklist. Velos eResearch will be used as the electronic clinical trials and data management system. Affiliate sites will enter data directly into Velos eResearch via customized case report forms for the study. The research staff will generate reports from Velos eResearch to ensure timely submission of data by affiliate sites. This resource allows for the timely analysis of particular data sets for safety analysis.

14. Record Keeping and Record Retention

The Principal Investigator is required to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects, as well as written records of the disposition of the drug when the study ends.

The Principal Investigator is required to prepare and maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. The case history for each individual shall document that informed consent was obtained prior to participation in the study. Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, CHR correspondence and approval, signed patient consent forms). Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.
In accordance with FDA regulations, the investigator shall retain records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated; or, if no application is to be filed or if the application is not approved for such indication, until 2 years after the investigation is discontinued and FDA is notified.

APPENDIX 6: PILL DIARY

Study IRB Number: AAAR1117

Patient Pill Diary

Patient name: _____ Patient study ID: _____

Number of pills given: _____ Total Daily Dose: _____

Pill Bottle(s) returned (Circle): Yes / No Number of Pills returned: _____

(To be completed by RN)

Guidance for Entinostat administration

- Entinostat should be taken in the morning, on an empty stomach, at least 2 hours after a meal and at least 1 hour before the next meal.
- The pills should be taken whole and not crushed.
- If you happen to vomit after taking a dose of medication, **do not take** an additional pill.
- If you have inadvertently missed a dose on scheduled day, the dose could be taken within 2 days of the scheduled dose.
- Please make all efforts to adhere to the dosing schedule.
- Please return all unused tablets and/or empty bottles to the clinic for accountability purposes.

Please complete the table below for Entinostat administration:

Day	Date	# of 5 mg (yellow) tablets taken	# of 1 mg (brown) tablets taken	Comments
Example	6/1/14	2	0	
Day 1	/ /			
Day 8 (if applicable)	/ /			
Day 15	/ /			
Day 22 (if applicable)	/ /			

Patient Signature_____ Date _____

Consenting Professional/Research RN Signature: _____ Date: _____

Comments:_____

_____

_____