THERAPEUTIC/DIAGNOSTIC PROTOCOL

A Phase I/II Clinical Study of Vorinostat in Combination with Etoposide in Pediatric Patients < 21 Years at Diagnosis with Refractory Solid Tumors

Vorinostat will be supplied by Merck & Co., Inc

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ABBREVIATIONS

4A4OA	4-anilino-4-oxobutanoic acid
AUC	Area under the curve
BID	Twice daily
CIB	Clinical Investigator Brochure
Cmax	Maximum concentration
CTCAE	Common Toxicity Criteria Adverse Event
CTEP	Cancer Therapy and Evaluation Program
CTLC	Cutaneous T-cell lymphoma
CYP	Cytochrome P450
DCC	Data and Coordinating Center
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
EFT	Ewing family of tumors
EKG	Electrocardiogram
FDA	U.S. Food and Drug Administration
[^{18}F]FDG	^{18}F-Fluorodeoxyglucose
HDAC	Histone deacetylase
MEL	Murine erythroleukemia
MSAS	Memorial Symptom Assessment Scale
MTD	Maximum Tolerated Dose
OG-V	*O*-glucuronide of vorinostat
POETIC	Pediatric Oncology Experimental Therapeutics Investigators Consortium
PPIs	Proton Pump Inhibitors
RECIST	Response Evaluation Criteria in Solid Tumors
RMS	Rhabdomyosarcoma
RP2D	Recommended Phase II Dose
RSA	Research Study Assistant
SAHA	Vorinostat
SAMF	Southern Alberta Microarray Facility
SPSS	Statistical Package for the Social Sciences
t ½	Half-life
TID	Three times daily
UGT	Uridine diphosphate glucuronosyltransferase isoenzymes
VEGF	Vascular endothelial growth factor

1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a multi-center, open label phase I/II trial evaluating the safety and efficacy of the novel regimen vorinostat and etoposide. In the Phase I portion, the primary objective will be to determine the dose limiting toxicity (DLT) and the maximum tolerated dose (MTD) for the combination vorinostat and etoposide in pediatric patients with relapsed/refractory solid tumors including tumors of the central nervous system. A standard dose escalation schema will be used with 3-6 subjects enrolled per dose level (cohort). Patients will be treated with vorinostat and etoposide primarily in the outpatient setting, although treatment as an inpatient will be permitted as long as eligibility criteria are met. The dose schedule will be comprised of escalation of the dose of vorinostat in increments of 30%. Vorinostat will be administered orally on Days 1-4 of every 21-day cycle and given 4 hours prior to the administration of etoposide on Days 3 and 4. The starting dose of vorinostat will be 50% of the single agent RP2D for the oral formulation. The etoposide will be administered intravenously at a fixed dose of 100 mg/m^2/day on Days 3-5 of every 21-dose cycle. Inter-patient dose escalation will proceed as follows until the MTD and RP2D is established:

DOSE ESCALATION SCHEDULE		
Dose Level	**Dose**	
	Etoposide (mg/m^2)	Vorinostat (mg/m^2)
-2	75	100
-1	100	100
1	100	125
2	100	160
3	100	210
4	100	270

Once the MTD level is determined, this level will be expanded to treat a total of 9 patients at the MTD to determine the safety of the RP2D. There will be no intra-patient dose escalation. An interim analysis for safety will be performed at the end of the phase I portion of this study. It is anticipated that the phase I component of the study will be completed within 1 year with an expected accrual of 18-25 patients.

Once the MTD and RP2D have been established and an interim safety analysis performed, the phase II portion of the trial will begin. The primary objective of the phase II component will be to determine the efficacy (CR+PR rate) of the combination vorinostat and etoposide in patients with relapsed/refractory sarcoma. Tumor measurements by Revised RECIST guideline (version 1.1) will be obtained every 2 cycles (every 6 weeks) according to section 12.0 to assess response. Subjects who achieve stable disease or better response to therapy will receive treatment until disease progression by RECIST, unacceptable toxicity or if the patient voluntarily withdraws from the study. It is anticipated that the phase II component of the study will be completed within 1 year with an expected accrual of 28 patients.

Secondary objectives of the study will include correlative studies evaluating the biologic effects of the novel combination of vorinostat and etoposide in pediatric patients enrolled on this study. Specifically, exploratory studies will be conducted to determine the changes in histone acetylation, gene expression profiling and histone phosphorylation in patients treated on this study. Functional imaging will be included as a secondary objective to evaluate alteration in the accumulation of [^{18}F]- fluorodeoxyglucose ([^{18}F]FDG) with tumor response.

An exploratory objective of this study will be the measurement of symptom distress in patients enrolled on this trial. It is hoped that these observations will provide unique insight into the changes children with relapsed/refractory solid tumors experience in symptom perception during treatment with investigational agents. In addition, these findings may help predict patterns of symptom distress and provide us with the opportunity to anticipate patients at risk for heightened symptom distress.

2.1 OBJECTIVES AND SCIENTIFIC AIMS

2.2 Primary Objectives

2.2.1 Part I: To establish the Dose Limiting Toxicity (DLT), Maximum Tolerated Dose (MTD), and the recommended phase II dose (RP2D) of the novel combination vorinostat and etoposide in pediatric patients with relapsed/refractory solid tumors including tumors of the central nervous system.

2.2.2 Part II: To establish the efficacy (CR+PR rate) of the novel combination vorinostat and etoposide in pediatric patients with relapsed/refractory sarcoma.

2.3 Secondary Objectives

2.3.1 To evaluate the efficacy (CR+PR rate) of the novel combination vorinostat and etoposide in pediatric patients enrolled in the phase I component of the study.

2.3.2 To evaluate the biologic effects of the novel combination of vorinostat and etoposide in pediatric patients with relapsed/refractory solid tumors including central nervous system tumors using Histone Acetylation, Gene Expression Profiling, and Histone Phosphorylation Profiling.

2.3.3 To correlate alterations in accumulation of [^{18}F]FDG with tumor response in patients for whom this imaging modality is relevant.

2.4 Exploratory Objectives

2.4.1 To describe symptom distress over time in pediatric cancer patients treated with the novel combination of vorinostat and etoposide in both parts of the study.

3.1 BACKGROUND AND RATIONALE

3.2 Sarcomas

Sarcomas comprise 15% of pediatric malignancies. In 2003, approximately 12,000 Americans were diagnosed with sarcoma and 5,200 died from the disease. These figures are probably underestimates as the number of Americans with each type of sarcoma subtype is unknown.

Osteosarcoma is the most common primary malignant bone tumor in children and adolescents. It is a highly aggressive neoplasm typically composed of spindle cells producing osteoid. The development of recurrent and/or metastatic disease depends on the initial therapy, time to recurrence, and the site and number of recurrent tumors. With aggressive treatment, 40% of patients who develop metastatic disease survive > 5 years after relapse. However, patients who relapse following the use of modern treatment approaches, including chemotherapy and surgery, have a significantly lower probability of survival. These patients are candidates for participation in clinical trials with novel agents.

The Ewing family of tumors (EFT) represents the second most common primary bone malignancy affecting children and adolescents. Patients who initially present with or develop metastatic disease have a significantly less favorable outcome than those with localized disease. Aggressive multimodality therapy can relieve pain, prolong the progression-free interval, and cure some patients of their disease; however, the 5- year overall survival rate averages 33%.

Soft tissue sarcomas are highly malignant tumors that constitute 5-6% of all malignant childhood neoplasms. Of these, rhabdomyosarcoma (RMS) is the most common in children. Many children with RMS are cured with conventional chemotherapy and local therapy: surgery with or without radiotherapy. Children with metastatic disease at presentation, particularly those with bone marrow or bone involvement have a much poorer outcome. The 5-year overall survival for patients with metastatic disease is approximately 25%.

Mortality rate remains disproportionately high when compared with other cancers common to these age groups such as testicular cancer and Hodgkin's disease. Diagnosis was delayed in many patients by the lack of experience of primary physicians, who often attribute the initial mass to common benign lesions. Once diagnosed, patients cannot rely on a uniform standard of care, resulting in wide variations in outcomes. Treatment options for patients with advanced pediatric malignancies are limited. New therapies are needed, but the fragmentation of biologic, translational, and clinical research makes it difficult to initiate innovative and timely studies.

This study will evaluate the role of a novel histone deacetylase inhibitor, vorinostat, in combination with the topoisomerase II inhibitor, etoposide in all pediatric tumors in the phase I component but will later focus on refractory sarcomas in the phase II component.

3.3 Vorinostat

3.3.1 Histone deacetylase and HDAC Inhibitors

Histone deacetylase (HDAC) are enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. HDAC inhibitors can induce tumor regression in animals. The transcription of genes is regulated at least in part by acetylation of nucleosomal histones. The core nucleosomal histones are the most widely studied of the proteins that become acetylated following inhibition of HDAC activity. In some tumor cells, there is an overexpression of HDACs or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypoacetylation of core nucleosomal histones. Hypoacetylation of histones is associated with a

condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation.

3.3.2 Mechanism of Action of Vorinostat

Vorinostat is a potent inhibitor of HDAC activity that binds directly to the catalytic pocket of HDAC enzymes. Vorinostat, at low nanomolar concentrations (IC_{50} < 86 nM), inhibits the enzymatic activity of HDAC1, HDAC2, and HDAC3 (Class I) and HDAC6 (Class II). The concentration of vorinostat that causes the accumulation of acetylated histones also induces cell cycle arrest, differentiation or apoptosis of transformed cells.

Vorinostat induces apoptosis in a wide variety of transformed cells in culture, including cutaneous T-cell lymphoma cell lines, circulating atypical T-cells derived from patients with CTCL, human lymphoma cell lines and murine erythroleukemia (MEL) cells. Vorinostat also inhibits proliferation of cultured transformed human cells derived from leukemias, non-small cell lung carcinomas, colon carcinomas, central nervous system tumors, melanomas, ovarian carcinomas, renal cell carcinoma, prostate and breast cancers. In cultured human transformed cell lines, vorinostat has synergistic or additive activity in combination with other cancer therapies, including radiation, kinase inhibitors, cytotoxic agents, and differentiating agents. In vivo, vorinostat demonstrates anti-neoplastic activity in a variety of rodent tumor models including xenograft models of human prostate, breast and colon carcinoma.

3.3.3 Nonclinical Pharmacology of Vorinostat

Vorinostat is approximately 71% bound to human plasma proteins over the range of concentrations of 0.5 - 50 μg/mL.

Vorinostat has a low propensity to cause or be affected by drug-drug interactions. In animal models and *in vitro* human systems, the major pathways of metabolism of vorinostat are glucuronidation and hydrolysis followed by β-oxidation. Additionally, the glucuronidation of vorinostat is mediated by multiple uridine diphosphate glucuronosyltransferase isoenzymes (UGTs), making it less susceptible to drug interactions through modulation of UGTs. Vorinostat is not recovered intact in urine to any appreciable extent. Therefore, compounds known to affect renal elimination are not expected to affect the pharmacokinetics of vorinostat.

Vorinostat is not an inhibitor (IC_{50} of > 75 μM) of CYP drug metabolizing enzymes in human liver microsomes. Gene expression studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 mRNA and enzyme activity levels were observed at ≥10 μM vorinostat following a 48 hr treatment period. However, these changes were observed at concentrations of vorinostat higher than pharmacologically relevant serum concentrations of 2 μM (C_{max}). Thus, vorinostat is not expected to affect the pharmacokinetics of other agents. As vorinostat is not eliminated via the CYP pathways, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs that are known CYP inhibitors or inducers. However, no formal clinical studies have been conducted to evaluate drug interactions with vorinostat. Please refer to vorinostat CIB for detailed information.

3.3.4 Nonclinical Toxicology of Vorinostat

Vorinostat has been investigated in nonclinical acute and oral repeated-dose toxicity studies, reproductive, developmental toxicity studies, and genetic toxicity studies to support oral administration of this compound to humans. The main toxicities observed in animal models were weight loss and inappetence, apparent hemolytic anemia (rats only at 3.6 times the equivalent 400 mg human dose), leukopenia (rats only at 1.3 times the equivalent 400 mg human dose), thrombocytopenia (male rats only, statistically significant change at 0.5 times the equivalent 400 mg human dose but within normal range at all doses), and gastrointestinal tract irritation (dogs only, at 8.5 times the equivalent 400 mg human dose). Although statistically significant and dose- dependent, many of the clinical pathology findings were within normal historical ranges indicating that they should not have major toxicological consequences. The toxicities appeared to be rapidly reversible within 12 to 14 days. There has been no evidence of cardiac toxicity based on electrocardiogram (ECG, dogs only), blood pressure (dogs only), heart rate (dogs only), creatinine kinase, organ weight, gross pathology, or histopathology assessments in studies up to one month duration. No serious, irreversible damage to any vital organ has been observed. Importantly, toxicities in rats and dogs were predictive of adverse effects in humans (anorexia, weight loss, fatigue). Toxicities present in animals would be manageable in the clinic, and the onset of serious toxicity is readily forecast by prodromal symptoms. The nonclinical toxicity profile of vorinostat is acceptable for an oncology drug. Vorinostat rapidly crossed the placenta in both the rat and rabbit, following administration of a dose of 15 mg/kg/day and 150 mg/kg/day, respectively (<1 times the human exposure based on AUC_{0-24}) and reached transplacental equilibrium within 30 minutes post-dose. Vorinostat was evaluated in a panel of genetic toxicity assays; in vivo and in vitro assays were found to be positive. Therefore, vorinostat should not be taken by pregnant women. Pregnancy should be avoided both in female subjects taking vorinostat, and in female partners of male subjects taking vorinostat for at least 30 days after last dose of vorinostat, as data are not yet available to establish the safety of vorinostat ingestion in male patients who impregnate their partners. No human safety data for the use of vorinostat during pregnancy are available. Please refer to the vorinostat CIB for detailed information

3.3.5 Clinical Pharmacokinetics of Vorinostat

The pharmacokinetics of vorinostat following 400 mg single-dose in a fasted state; and 400 mg single- and multiple-doses in a fed (high-fat meal) state were evaluated in 23 patients in a Phase I study with relapsed or refractory advanced cancer using a validated assay. {Rubin}. See Table 1.

Table 1					
PK Parameters of vorinostat following oral administration of single or multiple doses of 400 mg					
	400-mg Single Dose Fasted	**400-mg Single-Dose Fed**	**400-mg Multiple Dose Fed**	**GMR ¶**	**-Value**
N	23	20	14	--	--
AUC $_{0-\infty}$, **µM**·hr†	3.87	5.33	--	1.38#	< 0.001#
$_{0\text{-}24\ hr,}$ **µM**·hr†	3.82	5.33	6.46	1.21†† 1.23‡‡	0.019†† 0.010‡‡
C_{max}, **µM**†	1.12	1.02	1.13	0.91#	0.451#
T_{max}, hr ‡	1.50	4.00	4.21	--	<0.001ⁱ 0.869§§
$t_{1/2}$, hr§	1.74	1.44	1.34	--	0.036#
fe ‖	0.0021	0.0030	0.0037	--	--

fe = Fraction of dose excreted unchanged in urine
†Geometric mean
‡ Median
§ Harmonic Mean

" Arithmetic mean (single dose fasted N = 22, single dose fed N = 21, multiple dose fed N = 12).
¶ Geometric mean ratio.
# Single dose fed/single dose fasted.
†† Accumulation ratio: AUC0-24 hr multiple dose fed/AUC0-24 hr single dose fed.
‡‡ Linearity ratio: AUC0-24 hr multiple dose fed/AUC0-∞ single dose fed.
§§ Multiple dose fed/Single dose fed.

Vorinostat is eliminated predominantly through metabolism with less than 1% of the dose recovered as unchanged drug in urine, indicating that renal excretion does not play a role in the elimination of vorinostat. Recovery of two pharmacologically inactive metabolites, *O*-glucuronide of vorinostat (OG-V) and 4-anilino-4-oxobutanoic acid (4A4OA), in urine was more substantial. Please refer to the vorinostat CIB for detailed information.

3.3.6 Summary of Clinical Experience with Vorinostat

As of July 2, 2012, Vorinostat has been orally administered to more than 5,000 patients in Phase I, Phase II and Phase III clinical studies. These studies were sponsored by either Merck, Sharp & Dohme Corporation, a subsidiary of Merck & Co., Inc. (herein referred to as Merck), including MSD KK (Japan), in addition to the United States (U.S.) National Cancer Institute (NCI), the National Comprehensive Cancer Network (NCCN), or by Investigators participating in the Merck Investigator Studies Program (MISP). MISP clinical studies are small-scale clinical trials conducted and sponsored by an independent investigator for which Merck may provide support in the form of a supply of vorinostat or financial assistance. Vorinostat has been studied both alone and in combination with other chemotherapy agents.

Merck & Co., Inc. sponsored 30 clinical trials and independent Investigators have sponsored 85 clinical

trials with vorinostat. One thousand seven hundred and forty seven (1,740) patients have been treated with vorinostat alone or in combination with other chemotherapeutics in Merck & Co., Inc sponsored clinical trials. One thousand six hundred and seven (1,607) patients have been enrolled in investigator-initiated studies. In addition, 61 studies with vorinostat are ongoing, sponsored by the United States National Cancer Institute (NCI) under the Cancer Therapy Evaluation Program (CTEP) with one thousand seven hundred and eighteen (1,718) patients enrolled as of November 5, 2012. Therefore, over five thousand (5,000) patients have received at least one dose of vorinostat in studies sponsored by Merck the NCI, NCCN, or independent Investigators (MISP). Please refer to the vorinostat CIB for detailed information

3.3.7 Safety of Vorinostat

The total daily dose of vorinostat administered per patient ranged from 200 mg to 900 mg across all studies. The tolerability of vorinostat appears to be determined by total daily dose and the number of consecutive days of dosing. The administration frequency across all studies included once daily (QD) continuous dosing, twice daily (BID) continuous dosing, BID discontinuous dosing, and three times daily (TID) discontinuous dosing The maximum tolerated dose (MTD) for continuous daily dosing without a rest period is 400 mg daily or 200 mg twice daily (BID). The MTD for intermittent dosing has been established as 300 mg BID x 3 consecutive days per week, or 250 mg 3 times daily (TID) x 14 consecutive days followed by a 7-day rest period {127}.

Data are presented across all 30 Merck-sponsored protocols to examine the adverse experience profile in the overall population of study patients receiving vorinostat monotherapy and vorinostat in combination therapy. The clinical safety of vorinostat is supported by data from 1,740 patients and 1,744 patient exposures in CTCL monotherapy, CTCL combination therapy, hematologic malignancies monotherapy, hematologic malignancies combination therapy, solid tumor monotherapy, and solid tumor combination therapy populations. The additional patient-exposures occurred in the initial supportive CTCL study, where patients enrolled in one cohort were permitted to enroll in a subsequent cohort at a later time point. As a result, 4 patients participated in 2 dosing cohorts. While the total number of patients in the CTCL monotherapy population was 180, the total number of patient- exposures was 184.

Among all 1,740 patients (1,744 patient-exposures), adverse experiences assessed by the investigator as Grade 3 or higher were mainly seen in the system organ classes (SOC) of: blood and lymphatic system disorders; gastrointestinal disorders; general disorders and administration site conditions; investigations; metabolism and nutrition disorders; nervous system disorders; respiratory, thoracic, & mediastinal disorders; and skin and subcutaneous tissue disorders. The vorinostat safety profile across the different populations is not significantly different. Most of the common AEs experienced by ≥10% of all patients across the different populations are generally comparable. Three hundred and five (17.5%) patients have had SAEs that were considered by the Investigators to be possibly related to vorinostat. Thrombocytopenia was the most common drug-related SAE reported across all 30 Merck-sponsored studies and occurred in 39 (2.2%) patients. Overall, treatment with oral vorinostat was well tolerated. Pulmonary embolism and deep vein thrombosis have been reported. Investigators should be alerted to the signs and symptoms of these events. QT prolongation has been observed as well. Monitoring of electrolytes and EKGs at baseline and periodically during treatment is clinically indicated. Please refer to the vorinostat CIB for detailed information.

Dose-limiting toxicities (DLTs) of single agent vorinostat were mainly non-hematologic (anorexia, dehydration, diarrhea, and fatigue); hematologic toxicities are primarily anemia and thrombocytopenia, most of which were mild to moderate. The majority of these DLTs occurred within the first month on vorinostat. The DLTs were manageable because these toxicities resolved quickly after drug administration was interrupted

A phase I study of oral vorinostat was performed in children with recurrent or refractory solid tumors. Vorinostat was administered once daily at dose levels 180, 230, and 300 mg/m^2/day. The toxicity profile was similar to adult trials. Of 24 patients evaluable for toxicity, DLTs included a deep vein thrombosis noted in 1/6 patients treated at a dose of 180 mg/m^2/day and hypokalemia in 1/6 patients treated at 230 mg/m^2/day. DLTs at 300 mg/m^2/day include reversible hypokalemia (1), neutropenia (1), and thrombocytopenia (2). The recommended phase II dose in children was established at 230 mg/m^2/day. Additional Grade 3 or 4 non-dose limiting toxicities included elevation in ALT/AST, hyperbilirubinemia, leucopenia and lymphopenia.[7] A phase I study has been conducted with the oral vorinostat in combination with 13 cis-retinoic acid in children with refractory neuroblastoma, medulloblastoma, primitive neuroectodermal tumors and atypical rhabdoid tumor. Vorinostat was well tolerated at a dose of 180 mg/m^2/day for 4 days a week when administered with cis-retinoic acid at a dose of 80 mg/m^2/dose BID for 12 days of a 28 day course. [41] There have been no clinical trials conducted in children with vorinostat in combination with a cytotoxic agent to date.

3.3.8 Efficacy of Vorinostat

Vorinostat has recently been approved by the US FDA for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies.

3.3.8.1 Efficacy in Patients with Solid Tumors

In Protocol 002, a Phase II study of vorinostat in patients with head and neck cancer, no confirmed partial or complete responses were observed in the 12 patients enrolled in the study. An unconfirmed partial response was observed in one patient and stable disease was observed in three patients. In Protocol 006, a Phase I study of vorinostat in patients with advanced solid tumor and hematologic malignancies, 50 patients with solid tumors were enrolled. Tumor responses. and stable disease were noted in several patients with solid tumors, confirmed PR's were observed in patients with thyroid papillary carcinoma and squamous cell carcinoma of the larynx and 2 unconfirmed partial responses for patients with – mesothelioma. The confirmed responses occurred at 400 mg twice daily x7d/wk.

In a Phase I study evaluating the safety, tolerability, pharmacokinetics and pharmacodynamics of vorinostat in patients with advanced cancers, no formal efficacy evaluations were performed. The study concluded that short-term administration of vorinostat to patients with advanced cancer was generally well tolerated.

In a Phase II study of vorinostat in patients with relapsed or refractory breast, colorectal, and non-small cell lung cancer, the primary objectives of the protocol were to determine the response rate of anti-tumor efficacy using RECIST criteria and to evaluate positron emission tomography (PET) as an early indicator of response to vorinostat at the initial starting dose of 400 mg po BID for 14 of 21 days. The efficacy evaluation included all patients who received 14 days of continuous study therapy and PET scans performed on Day 15. A total of 16 patients were enrolled. Seven (7) patients were reported to

have a best response of SD. Of the patients with SD, 1 patient had breast cancer and the remaining 6 patients had lung cancer. No patients were observed to have a best response of partial or complete response. Please refer to the vorinostat CIB for detailed information.

3.3.8.2 Efficacy in Patients who Received Combination Therapies

Vorinostat is eliminated predominantly through metabolism with less than 1% of the dose recovered as unchanged drug in urine, indicating that renal excretion does not play a role in the elimination of vorinostat. Recovery of two pharmacologically inactive metabolites, O-glucuronide of vorinostat (OG-V) and 4-anilino-4-oxobutanoic acid (4A4OA), in urine was more substantial. Please refer to the vorinostat CIB for detailed information.

In PN056, a phase II/III randomized double-blind study of paclitaxel and carboplatin in combination with vorinostat or placebo in patients with stage IIIB (with pleural effusion) or stage IV non-small cell lung cancer, 253 patients were enrolled. The study was stopped following a pre-planned interim analysis because the goal for this study to continue was not met, based on 100 events, a reduction in the hazard ratio for progression-free survival by >23% with a one-sided p-value <0.1.

In PN058, a phase I clinical study of vorinostat in combination with gemcitabine and cisplatin in patients with advanced non-small cell lung cancer, 61 patients were enrolled. Of the 49 patients included in the efficacy analysis, across five dose cohorts, 13 had an objective overall response.

In PN066, a phase I clinical study of vorinostat in combination with carboplatin and paclitaxel conducted in Japan (MSD KK) in patients with advanced non-small cell lung cancer, 3 patients were enrolled. All 3 patients experienced dose limiting toxicities during cycle 1 so no efficacy data was be available for this study

3.4 Etoposide

Etoposide (VP16), a semisynthetic derivative of podophyllotoxin, acts as a topoisomerase II inhibitor. It is a cell-cycle, phase-specific drug which has demonstrated activity in the phase II setting in treating a broad spectrum of pediatric and adult malignancies. Single-agent activity for pediatric solid tumors of approximately 20% with variation in the disease specific response rates (ie., osteosarcoma 9%, soft tissue sarcoma 8%, rhabdomyosarcoma 19%, and Ewing's sarcoma 40%). In most pediatric and adult salvage regimens, etoposide is usually administered intravenously at a dose of 100-200 mg/m^2/day for 3-5 days every 3 weeks in association with other drugs, i.e., cyclophosphamide, ifosfamide and platinum derivatives. In this study, vorinostat will be added to etoposide to see if the anti-tumor activity will improve upon that seen with single agent etoposide alone. Data mainly in adults with small cell lung cancer suggested that low dose prolonged administration appears to be at least as effective as higher doses over a short period with better tolerance.

3.5 Rationale for Combination Therapy with Vorinostat and Etoposide

Vorinostat has been shown to induce cell cycle arrest, differentiation, and apoptosis in a variety of adult and importantly in pediatric tumors including neuroblastoma and rhabdomyosarcoma. [13-17] Extensive preclinical studies have demonstrated evidence of anti-tumor activity of this agent in combination with a variety of agents including topoisomerase II inhibitors (ie. etoposide, doxorubicin) [18, 19], DNA

hypomethylating agents (ie., 5-azacytidine or decitabine) [20] , Imatinib mesylate[21-23] , Bortezomib [24] , Ellipticine [19], Cisplatin [25] and Hsp 90 inhibitors [26] . Of interest, vorinostat has been shown to potentiate DNA damage induced by topoisomerase II inhibitors in a sequence-specific fashion. Pre-treatment with Vorinostat 48 H prior to exposure to a topoisomerase II inhibitor has been shown to be synergistic in breast cancer cell lines.[27] Enhanced cytotoxicity has also been demonstrated with other chemotherapeutic agents including ellipticine, doxorubicin, or cisplatin, but not of the topoisomerase I inhibitor camptothecin.[19] However, treating cells in the reverse order (anticancer drug followed by vorinostat) was no more cytotoxic than the anticancer drug alone. Additional unpublished data by Dr. Aru Narendran, an investigator in this trial demonstrated similar results with the combination of vorinostat and etoposide. First, drug sensitivity curves for etoposide were determined then leukemic cells were cultured with increasing concentrations of vorinostat alone or in combination with etoposide at its IC_{10} or IC_{25} values. In these experiments, etoposide was added at the same time, 48 hours after the addition of vorinostat. After four days in culture, cell growth inhibition was quantified by Alamar blue assay. The fraction affected (Fa) and the combination index (CI) were calculated with the CalcuSyn computer program (Biosoft) according to the method of Chou and Talalay.[2] Results shown in Figure 1 show the representative findings from the cell line C1 demonstrating synergistic effect when etoposide was added after 48 hours with a calculated CI of 0.64 compared to the final cytotoxicity when the two agents were added together (CI = 1.1).

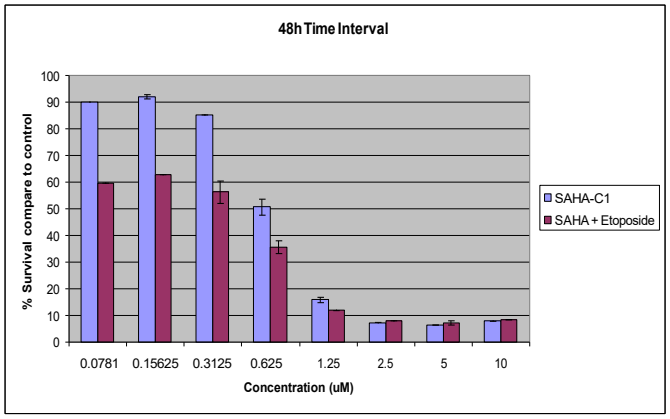

Figure 1. Cytotoxicity of Vorinostat and Etoposide in Leukemia

Phase I has been completed and the combination Vorinostat and Etoposide has demonstrated a favorable toxicity profile in patients with relapsed/refractory solid tumors, including tumors of the central nervous system

We will evaluate in a phase II trial the safety of vorinostat in combination with the topoisomerase II inhibitor etoposide in pediatric patients with relapsed/refractory sarcoma tumors.

3.6 Correlative Studies

The study will incorporate biologic correlative analyses to evaluate the following: assessment of histone acetylation/gene expression profiling and assessment of cellular phosphorylation profiling. Incorporation of these correlative studies we hope will enhance our understanding of histone deacetylation and the

ensuing anti-tumor activity in sarcoma patients treated with the proposed novel combination, vorinostat and etoposide.

Histone Acetylation and Gene Expression Profiling

Molecular studies of clinical samples obtained from patients with cancer can provide rich clinical and biological information. Gene expression profiling of diagnostic breast cancer samples has been used to identify expression profiles associated with risk of metastasis [28, 29] (van't Veer el al., 2002; van de Vijver, et al., 2002). In this protocol, pre- and post-treatment samples of tumor will be collected for correlative molecular studies. These samples will be used to search for (1) gene expression profiles that predict response to the combination vorinostat and etoposide; (2) expression changes that occur after exposure to Vorinostat and Etoposide. Results from these gene expression studies may provide important information regarding the mechanisms of response to vorinostat. Ultimately, these results could guide the selection of patients for treatment with vorinostat.

Histone Phosphorylation Profiling

Vorinostat and another HDAC inhibitor, depsipeptide, have shown efficacy in a wide range of cancers, in particular for cutaneous T-cell lymphoma (CTCL), and are progressing in phase II clinical studies. However, evidence is accumulating that specific HDAC enzymes are important with respect to clinical efficacy, calling the usefulness of the classical inhibitors into question. Class I enzymes are being heralded as the most clinically relevant; however, mechanisms involved in these processes are currently not clear. [30, 31]

Class IIa histone deacetylases (HDACs) are found both in the cytoplasm and in the nucleus where they repress genes involved in several major developmental programs. [32] In response to specific signals, the repressive activity of class IIa HDACs is neutralized through their phosphorylation on multiple N-terminal serine residues and 14-3-3-mediated nuclear exclusion. It has been shown that class IIa HDACs are subjected to signal-independent nuclear export that relies on their constitutive phosphorylation. EMK and C-TAK1, two members of the microtubule affinity-regulating kinase (MARK)/Par-1 family have been identified as regulators of this process.[31] It has been shown that EMK and C-TAK1 phosphorylate class IIa HDACs on one of their multiple 14-3-3 binding sites and alter their subcellular localization and repressive function.

Using HDAC7 as a paradigm, it has been demonstrated that signal-independent phosphorylation of the most N-terminal serine residue by the MARK/Par-1 kinases, i.e., Ser155, is a prerequisite for the phosphorylation of the nearby 14-3-3 site, Ser181. This shows that multi-site hierarchical phosphorylation by a variety of kinases allows for sophisticated regulation of class IIa HDAC function. [31]

We propose to investigate target modulation patterns in peripheral blood lymphocytes in response to specific anti-tumor activity of Vorinostat. This is based on the rationale that vorinostat inhibits its target enzyme (HDAC) in peripheral mononuclear cells while exerting its activity on tumor tissue.[13] The anti-tumor activity of HDAC inhibitors has been attributed to both their ability to inhibit deacetylases and their capacity to down-regulate phenotypic expression of oncoproteins as well as activation of the intrinsic apoptosis-inducing cascade. [32-35] It has been shown that cell cycle arrests or induction of apoptosis are dependent on treatment conditions such as drug concentrations and duration of drug exposure, as well as the intrinsic sensitivity of malignant cells to this class of anticancer agents.[36] In

addition, HDAC inhibition has been shown to induce acetylation and inhibit the ATP binding and chaperone function of heat shock protein (HSP) 90. This promotes the polyubiquitylation and degradation of the pro-growth and pro-survival client proteins such as FLT-3, Raf and AKT.[37]

In the mantle cell lymphoma model, HDAC inhibitors have been shown to reduce VEGF production and to induce growth suppression of the malignant cells. [38] Effects of HDAC inhibition also lead to decreased expression of angiogenesis-related genes such as angiopoietin-2, Tie-2, and survivin in endothelial cells and down-regulated hypoxia-inducible factor 1-alpha and VEGF expression in tumor cells. [39, 40] Based on these data, we hypothesize that the analysis of cell cycle regulators, apoptosis related proteins, clients of Hsp90 and angiogenesis related molecules in the peripheral mononuclear cells of patients undergoing therapy would provide effective target modulation analysis for this protocol.

3.7 Exploratory Objectives

Symptom distress

Symptoms are "perceived indicators of change in normal functioning as experienced by patients".[42] Lenz et al suggest that each symptom can be conceptualized as a multidimensional experience which can be described and measured separately by individuals.[42] Symptoms possess common dimensions such as intensity (strength or severity), timing (duration and frequency of occurrence), level of perceived distress (degree of discomfort or bothersome) and quality. Symptom distress is defined as the amount of physical or mental upset, anguish, or suffering experienced by an individual in relation to specific symptoms [43, 44]. Lenz et al proposes that symptom distress is the degree to which a person is bothered by the symptom and asserts that it is the dimension that contributes most to quality of life and is the most influential dimension in treatment decisions. Lenz et al suggest that the degree of symptom distress felt by an individual in relation to one symptom may be different if it is experienced in the presence of other symptoms. Furthermore, Lenz et al suggest that the concurrence of multiple unpleasant symptoms is likely to result in an experience that is multiplicative rather than additive. This has significance for cancer patients who experience a variety of unpleasant symptoms related to their disease and associated treatments.

Symptom clusters

Depending on a particular disease or treatment type, patterns of symptoms emerge. It is this grouping of symptoms that define symptom clusters. While individuals are able to distinguish the unique qualities of each symptom, the concurrent experience of multiple symptoms appears to have an effect that is greater than, and different from, the effect of each individual symptom alone. This phenomenon has been demonstrated in studies examining the effect of symptoms on quality of life [45, 46, 47]

Symptom Clusters and Symptom Distress in Children with Cancer

Although pediatric cancer clinical trials traditionally have focused on survival or toxicity, there is an emerging interest in the measurement of outcomes that reflect the impact of treatment on patients and therefore, their quality of life. This interest is related both to the improved survival of children with cancer and to a consensus that quality of life outcomes are highly relevant. [48, 49]

The distressing symptoms caused by childhood cancer and the associated treatments occur frequently due to aggressive therapy regimes implemented to cure the disease. The measurement of these

symptoms is important to understanding the effect of treatment on a child's quality of life. The intensity of these symptoms may ultimately influence the child and adolescent's ability to meet important developmental challenges and milestones. Therefore, attention must be given to the symptom experiences that occur during childhood cancer treatment so that we may decrease their distress and promote the needed energy for engaging in normal activities of childhood and adolescence. [50]

There is much still to be learned about the symptoms pediatric cancer patients experience and the effect of these symptoms on their quality of life. Few studies have attempted to describe the experience of symptoms in children with cancer. This is due, in part, to the lack of validated symptom assessment scales for this population. [51] Only recently have studies begun to address the distressing cancer events and symptoms from the perspective of the child and the family. Collins, et al in 2000 described the most common physical symptoms in a group of 160 children with cancer as lack of energy, pain, drowsiness, nausea, coughing, and lack of appetite.[48] In 2003, Hedstrom et al discovered that the most common causes of distress in a group of 121 children with cancer were treatment related pain, nausea and fatigue rather than the cancer itself. [52] Woodgate and Degner evaluated expectations and beliefs about childhood cancer symptoms in a group of 39 children and their families that showed that these individuals expected to experience suffering as part of the cancer treatment, even believing that unrelieved symptoms were necessary for the cure. [53] In a review of the research program at Texas Children's Hospital, it was demonstrated that fatigue, sleep disturbances, and pain are significant symptoms experienced by children. They also found an association between these symptom clusters and physical performance changes as well as behavior problems. It was also at Texas Children's Hospital that the Memorial Symptom Assessment Scale (MSAS) was reviewed and modified by experts in developmental pediatrics and pain management resulting in the development of tools specific for children in two separate age groups: the MSAS (10-18) and the MSAS (7-12). [54]

At present, there is no published data regarding multi - symptom assessment in a Phase I/II setting. In this study, we will use the MSAS (10-18) instrument to assess symptom complexes in relation to the novel chemotherapy regimen, vorinostat and etoposide.

This exploratory study may potentially lead to more definitive studies to establish a correlation between the symptom complexes and quality of life in children and adolescents on early clinical trials. The primary focus of these exploratory studies will be to determine whether symptom distress differs over time in children with relapsed/refractory sarcoma receiving vorinostat and etoposide.

This study will provide unique insight into the changes children with relapsed or refractory sarcoma experience in symptom perception during treatment with vorinostat and etoposide. In addition, findings may help us predict patterns of symptom distress and provide us with the opportunity to anticipate patients at risk for heightened symptom distress. Effective clinical practice should be based on accurate assessments and anticipation of needs. In order to do this, the first step is identifying symptoms and their pattern of manifestation. Findings from this study will accomplish this. Future strategies include applying interventions known to be effective in the management or prevention of symptoms or testing the efficacy of newly developed interventions that may prevent or minimize specific symptoms

4.1 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.2 Design

Part 1: Dose Escalation Phase

This is a multi-center, open label, phase I trial of escalating doses of vorinostat in combination with etoposide. This component of the study is designed to establish the MTD, DLT, and the RP2D of the combination vorinostat and etoposide in pediatric patients with relapsed/refractory solid tumors. Patients will be assessed in 3-week cycles. Escalating doses of vorinostat will be administered orally on a daily x 4 schedule in combination with a fixed dose of etoposide. Etoposide will be administered intravenously daily x 3 days. Cohorts of 3-6 patients will be treated with vorinostat and etoposide. The dose escalation schema for vorinostat is summarized in Section 9.3.

A minimum of 2 evaluable patients will be entered at each dose level. Dose escalation will not be considered until at least 3 patients at a given dose level have completed one course of therapy (e.g. 3 weeks) without a DLT. For the purposes of this study, DLT will be defined during the first cycle of treatment. The individual parameters of DLTs are defined in Section 9.7.

If a patient does not experience a DLT as defined in Section 9.7 but is taken off study due to unacceptable adverse events/toxicity, that patient will be considered to have had a DLT for the purposes of dose escalation. If therapy is discontinued during the first cycle for reasons other than toxicity, an additional patient may be enrolled at the dose level of the off-study patient to ensure adequate evaluation of toxicity.

The MTD is defined as the highest dose level with an observed incidence of DLT in no more than one out of six patients treated at a particular dose level. The dose escalation scheme is as follows:

The dose escalation scheme is as follows:

1) If none of initial three patients at a given dose level experience DLT, the next dose level is studied in another cohort of three patients.

2) If one of the initial three patients at a given dose level experience DLT, up to three additional patients will be treated at that same dose level. Escalation will continue if one of the six patients experience DLT.

3) If two or three patients experience DLT in the first three patients, or two or more patients experience DLT in six patients at a given dose level, the MTD will be determined as the preceding dose level.

4) If three or fewer patients are treated at a dose under consideration as the MTD, additional patients to total six will be treated at that level to confirm the MTD.

Once the MTD level is determined, this level will be expanded to treat a total of 9 subjects to determine the safety of the RP2D. If two (or more) of the 3-6 subjects, or 3 of the 9 subjects treated at a particular dose level experience a DLT at any time during the first cycle, then the MTD will have been exceeded.

Table 2

NUMBER OF PATIENTS WITH DLT AT A GIVEN DOSE LEVEL	ESCALATION DECISION RULE

0 of 3	Enter 3 patients at the next dose level.
≥2 of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 of 3	Enter at least 3 more patients at this dose level. If 0 of these 3 patients experience DLT, proceed to the next dose level. If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose.
≤1 of 6 at highest dose level below the maximally administered dose	This is generally the MTD. At least 6 patients will be entered at the MTD.

For those patients with measurable disease, response evaluation should be performed following every two cycles of treatment (> 4 and < 6 weeks from the start of the first cycle of treatment). The determination of antitumor efficacy in patients will be based on an objective tumor assessment made according to RECIST. An interim analysis will be performed by the Study Committee after Part 1 is completed and prior to initiation of the Part 2 (Phase II component) of the study.

Part 2: Efficacy Phase

This is a multi-center, open label phase II trial. The purpose of this component of the study is to establish the efficacy (CR+PR rate) of the novel combination vorinostat and etoposide in pediatric patients with relapsed/refractory sarcoma. Patients will be treated at the RP2D established for the combination vorinostat and etoposide in Part 1 of the study, which was found to be 270 mg/m^2/dose of Vorinostat and 100 mg/m^2/dose of Etoposide. The determination of antitumor efficacy will be based on objective tumor assessment made according to RECIST defined in section 12.0.

4.3 Intervention

Refer to Section 9.0

4.4 Number of Patients

Phase I Component: Approximately 18-25 patients will participate in this component of the study.
Phase II Component: Approximately 15-28 patients will participate in this component of the study.

4.5 Centers

This multi-center study will be conducted in 11 participating centers of the Pediatric Oncology Experimental Therapeutics Investigators' Consortium (POETIC) These institutions include All

Children's Hospital, MD Anderson Cancer Center, Memorial Sloan-Kettering Cancer Center, Phoenix Children's Hospital, Sidney Kimmel Cancer Center (Johns Hopkins Medical Center), Alberta Children's Hospital, Children's Hospital Colorado, Pennsylvania State University College of Medicine, Dana-Farber Cancer Institute, Children's Mercy Hospital & Clinics and Arnold Palmer Hospital for Children/MD Anderson Cancer Center Orlando.

4.6 Exploratory Studies

Symptom Distress

A descriptive, longitudinal study design will be conducted to prospectively compare the effect of the novel combination of vorinostat and etoposide on symptom distress in children, ages 10 – 18, enrolled on study using the MSAS (10-18) during routine visits to the outpatient clinic. [48, 51] At the pre-study visit and at the time of each radiographic evaluation (every 5 weeks + 7 days), the instrument will be given to the patient to complete in a private area with assistance from the research nurse or trained RSA in completing it. The research nurse or trained RSA will assist the participant in completion of the instrument thereby ensuring consistency across administration as well as completeness of the data collected. Completion of the questionnaire will take approximately 10-15 minutes. The time points for assessment have been selected in accordance with key time periods during treatment. A copy of this assessment will be submitted to the POETIC DCC along with the CRF's from the corresponding cycle as defined in section 16.0 of the protocol.

Symptom distress will be measured with the MSAS (10-18) [48] self-report instruments that measure the presence, frequency, severity and level of distress in children with cancer. The MSAS (10-18) measures 30 symptoms derived from a multidimensional symptom assessment instrument validated for use with adults. For each symptom, separate 4-or 5 point Likert scales were used to measure the dimensions of frequency, severity and distress. Twenty-two symptoms will be evaluated for each of the three dimensions; frequency was not relevant for eight symptoms and for these only severity and distress are assessed. Scoring of the MSAS yields several valid subscores, assessing psychological symptoms, physical symptoms and a global distress scale. Finally, the total MSAS score will be computed as an average of the symptom scores for all 30 symptoms across all applicable dimensions, whereby each symptom score is an average of the dimensions A high score will indicate a high level of symptom distress.

Descriptive statistics will be used to examine the effect of treatment and time on symptom distress.

5.1 THERAPEUTIC/DIAGNOSTIC AGENTS

5.2 Vorinostat

5.2.1 Formulation

Vorinostat (N-hydroxy-N'-phenyl-octane-1,8-diotic acid diamide, N hydroxy-N'-phenyl (9CI) octanediamide, suberoylanilide hydroxamic acid, also known as SAHA, or MK-0683), is an orally available HDAC inhibitor. The physical and chemical properties of vorinostat are listed in Table 3.

Table 3

MOLECULAR FORMULA	$C_{14}H_{20}N_2O_3$
Molecular Weight	264.32
Physical Appearance	White to light orange powder
Moisture (Karl Fischer) HPLC†	Maximum of 0.3% Single peak in reference system, Rt = 12.0 min
Melting Point	159.5 to 160.5 °C
PKa	9.2
Ultraviolet Absorption	λ_{max}= 242 nm (in methanol)
Hygroscopicity	Non-hygroscopic
Hydrates	None
Chirality	None
†HPLC = high pressure liquid chromatography. Rt = retention time.	

The oral formulation of vorinostat is available as a 100-mg capsule. Each 100 mg vorinostat capsule for oral administration contains 100 mg vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin and may contain sodium lauryl sulfate.

5.2.2 Labeling and Packaging

5.1.2.1 Patient Information

Vorinostat will be packaged in an open-label fashion. Clinical supplies will be packaged to support enrollment of approximately 50 patients.

5.2.3 Product Descriptions

Investigational material will be provided by Merck & Co., Inc. as summarized in Table 4**.**

Table 4
Product Descriptions

PRODUCT NAME & POTENCY	DOSAGE FORM	COMMENTS
Vorinostat 100 mg	Capsule	

5.2.4 Primary Packaging and Labeling Information

Vorinostat clinical supplies will be packaged in HDPE (high-density polyethylene) bottles as described in Table 5.

Table 5
Packaging of Clinical Supplies

PRODUCT NAME & POTENCY	FILL COUNT	DOSING INSTRUCTIONS
Vorinostat 100 mg	120 capsules	Take as directed by your study physician

5.2.5 Clinical Supplies Disclosure

This study is open-label; therefore, the patient, the Investigator, and site personnel are not blinded to treatment. Drug identity for vorinostat is included in the label text. Disclosure envelopes are not provided.

5.2.6 Investigational Agent Management

FDA regulations require investigators to establish a record of the receipt, use, and disposition of all investigational agents. The investigators in this study have the responsibility to assure the FDA that systems for agent accountability are being maintained by investigators in the clinical trials network. Investigators may delegate responsibility for agent ordering, storage, accountability and preparation to a designee in their institutions. However, the investigator is ultimately responsible for all agents shipped in his/her name. The intent of agent accountability is to assure that supplied agents are only used for patients enrolled on this trial. Investigational agents will not be shipped to a site unless all site and study specific regulatory documents have been received by the POETIC Data and Coordinating Center (DCC). The POETIC DCC will notify the site of their activation and provide clearance to order study drug from Fisher Clinical Sciences.

Requests and Shipping

Upon site activation by the POETIC DCC, the site will complete a Drug Shipment Authorization form (Appendix VI) and submit to the POETIC DCC. Sites may submit the authorization form for subsequent shipments to Fisher Clinical Sciences at the address listed below:

Fisher Clinical Sciences
Distribution Study Administration
7554 Schantz Road
Allentown, PA 18106
Phone: 610-871-8300
Fax: 610-871-8590
E-mail: distribution.allentown@Thermofisher.com

The information needed for completion of the Drug Shipment Authorization form is the POETIC protocol number, address, product information and quantity. The POETIC protocol, **POE10-02**, is included on the form. Investigational agents will only be shipped to the investigator's designated shipping address. All changes to the shipping address must be in writing and signed by the investigator or designee. The amount of drug requested will be in quantities of 3 bottles per order (each bottle contains 120 capsules), which will provide a supply for treatment of 3 patients for 2 cycles.

Requests for investigational agents for new subjects should be submitted the day of registration and no less than 3 business days prior to the start of treatment. Requests for subsequent cycles should be made a minimum of 1 week prior to treatment. Telephone requests will not be accepted.

Investigational agents will only be shipped to the investigator's designated shipping address. All changes to the shipping address must be in writing and signed by the investigator or designee.

Upon receipt of the drug supply, the site must verify and document that correct agent(s), lot numbers, and quantity were received in adequate shipping conditions. Once verified the Packing Slip (Appendix IV) must be completed, signed and returned to Fisher Clinical Sciences to the following contact and FAX: AOR Administrator, FAX# 610-871-0775. If there are problems with the shipment, the Site must notify the AOR Administrator immediately.

If there are any additional problems contact:

Gregg J. Rieker
Distribution Project Manager
Thermo Fisher Scientific (Fisher Clinical Sciences)
700 Nestle Way
Breinigsville, PA 18031
Phone: 484-538-2139
Fax: 610-871-0711
gregg.rieker@thermofisher.com

Agent Transfer, Return, or Destruction

Transfer of investigational agents between sites is prohibited unless approved by the DCC and the pharmaceutical management for drug distribution prior to the transfer.

Investigational agents are not interchangeable with approved commercial agents. Correct stock must be used for all doses, if investigational agent is not available for a subject at the scheduled time the subject's appointment must be changed.

Every effort should be made to minimize the amount of agent ordered and returned unused. Unused agents will either be returned or destroyed on-site as directed by the study staff when the study is completed or discontinued; agent is outdated, damaged or unfit for use. Opened or partially used vials/bottles are not to be returned unless specifically requested otherwise in the protocol. Broken vials are to be destroyed at the site, not returned.

If return of investigational agent is not required, the agent will be treated as chemotherapy or biological hazardous waste as appropriate and disposed of in accordance to the policies for hazardous waste management at the Site.

For agents destroyed on-site, the DAR must be completed and faxed to the POETIC DCC. If the investigational agent is returned, the completed DAR must accompany the agent.

Sites must maintain copies of all Requests for Drug Shipment, Packing Slips, and DARs on site,

available for monitoring and auditing until final closure of the study. After final closure of the study, forms may be stored off site as per the policy of the site.

5.2.7 Storage and Accountability

Documentation (receipt, transfer, dispensing, or return) will be maintained on the NCI Investigational Drug Accountability Record (DAR) (Appendix VII). Alternative accountability records may be provided to meet study specific requirements (example – oral medication involving return of meds by patient) beyond the DAR form's capability. A copy of the appropriate accountability record will be sent with the investigational agent.

A DAR must be maintained at each location an agent is stored (example – main pharmacy, satellite, etc). A separate DAR will be maintained for each protocol. Protocols using more than one supplied agent or more than one strength or formulation of the same agent, each agent, strength, and formulation will be stored separately and a separate DAR maintained. Proper completion of the DAR is mandatory, failure to complete all fields as required may prevent future shipments until it is determined appropriate accountability can be maintained. Audit of the DAR will be included in the monitoring visits of studies with investigational agents. All investigational agents will be stored as per manufacturer recommendations in a secure location away from commercial drug stock that is only accessible to authorized personnel. Each agent is to be stored and accounted for separately by protocol.

Investigational agents requiring storage in refrigerator or freezer must be stored within the temperature range required by the manufacturer upon receipt. The agents must be stored separately by protocol within the refrigerator/freezer. No food products may be stored within the refrigerator/freezer. A thermometer or monitoring device must be utilized to monitor and record temperatures on a log posted on the equipment at a minimum of once daily. Out of range temperatures must be documented with reason for situation and actions taken to correct.

Investigational agents must not be prepared until the subject is present, required testing completed, and the treating physician's orders are received. The investigator will administer the agent only to subjects registered to the study and under the investigator's personal supervision or under the supervision of a sub-investigator responsible to the investigator**.**

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate. Direct contact of the powder in vorinostat capsules with the skin or mucous membranes should be avoided.

If such contact occurs, wash thoroughly as outlined in the references. Personnel should avoid exposure to crushed and/or broken capsules. Please refer to the published guidelines regarding the handling of anticancer agents (refer to Vorinostat CIB).

5.3 **ETOPOSIDE** (VePesid®, Etopophos®, VP-16) NSC #141540

5.3.1 Formulation:

Commercial supply will be used for this study. Etoposide for Injection is available in sterile multiple dose vials. The pH of the clear, nearly colorless to yellow liquid is 3 to 4. Each mL contains 20 mg

etoposide, 2 mg citric acid, 30 mg benzyl alcohol, 80 mg modified polysorbate 80/Tween 80, 650 mg polyethylene glycol 300, and 30.5 percent (v/v) alcohol. Vial headspace contains nitrogen.

Etoposide phosphate for injection is available for intravenous infusion as a sterile lyophilized powder in single-dose vials containing etoposide phosphate equivalent to 100 mg etoposide, 32.7 mg sodium citrate USP, and 300 mg dextran 40.

5.3.2 Storage

Unopened vials of Etoposide are stable until expiration date on package at room temperature (25°C). Etoposide phosphate must be stored under refrigeration 2°-8°C (36°- 46°F). Unopened vials of etoposide phosphate are stable until the expiration date on the package.

5.3.3 Solution Preparation/Handling

Dilute Etoposide to a final concentration <0.4 mg/mL in Dextrose or Normal Saline containing IV solutions.

Etoposide Phosphate:

Dilute the 100 mg vial with 5 or l0 mL of Sterile Water for Injection, USP; 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; Bacteriostatic Water for Injection with Benzyl Alcohol; or Bacteriostatic Sodium Chloride for Injection with Benzyl Alcohol for a concentration equivalent to 20 mg/mL or 10 mg/mL etoposide (22.7 mg/mL or 11.4 mg/mL etoposide phosphate) respectively.

Following reconstitution, etoposide phosphate may be further diluted to concentrations as low as 0.1 mg/mL etoposide with Dextrose or Saline infusion solutions. Etoposide Phosphate may be administered as a bolus or by IV infusion.

5.3.4 Stability

Etoposide infusions are stable at room temperature for 96 hours when diluted to concentrations of 0.2 mg/mL; stability is 24 hours at room temperature with concentrations of 0.4 mg/mL. The time to precipitation is highly unpredictable at concentrations > 0.4 mg/mL.

5.3.5 Administration

Administer IV over 60 minutes (+ 10 minutes). **Do not administer etoposide by rapid intravenous injection.**

To avoid leaching of DEHP from PVC bags and tubing, prepare the Etoposide solution as close as possible preferably within 4 hours to the time of administration or alternatively as per institutional policy, non-PVC containers and tubing may be used.

When reconstituted with diluent containing a bacteriostat, etoposide phosphate solutions can be stored in glass or plastic containers under refrigeration at 2°-8°C (36°-46°F) for 7 days or at controlled room temperature 20°-25°C (68°-77°F) for 48 hours; following reconstitution with Sterile Water for Injection, USP, 5% Dextrose Injection, USP, or 0.9% Sodium Chloride USP store at controlled room temperature 20°-25°C (68°-77°F) for 24 hours.

5.3.6 Availability

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

6.1 CRITERIA FOR SUBJECT ELIGIBILITY

6.2 Subject Inclusion Criteria

6.2.1 Phase I Component: Histologic confirmation of relapsed/refractory solid tumors, including tumors of the central nervous system that have failed to respond to standard therapy, progressed despite standard therapy, or for which standard therapy does not exist. Patients with diffuse pontine glioma are not required to have histologic confirmation of disease, and are eligible with radiologic confirmation.

Phase II Component: the population will be restricted to relapsed/refractory sarcomas.

6.2.2 Patient must be between 4-21 years of age at the time of study enrollment. Efforts will be made to enroll patients <13 years of age so that adequate information about the biologic effects of this agent in younger patients can be obtained.

6.2.3 Patient must have Karnofsky ≥ 60% for patients >10 years of age; Lansky Play Scale ≥ 60 for children ≤ 10 years of age (see Appendix I).

6.2.4 Patient must have a life expectancy of > 8 weeks.

6.2.5 There is no limit to the number of prior treatment regimens provided that performance status and life expectancy meet the criteria above.

6.2.6 Normal organ and marrow function as defined below:

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1000 / mcL
Platelets	≥100,000 / mcL (transfusion not permitted)
Hemoglobin	≥ 9 g/dL qualifications (transfusion permitted)
Coagulation Prothrombin Time or INR	≤ 1.5x upper limit of normal (ULN)
Renal	
Serum creatinine or calculated creatinine clearance[a]	≤ 1.5x upper limit of normal (ULN) **OR** calculated creatinine clearance ≥ 60 mL/min for patients with creatinine levels > 1.5x institutional ULN.
Hepatic	
Serum total bilirubin	≤ 1.5 x ULN. Patient's who don't meet this criteria must have a Direct bilirubin ≤ 1.5 x ULN.
AST (SGOT) and ALT (SGPT) Alkaline Phosphatase (liver fraction)	≤ 2.5 x ULN. If AST or ALT is > 2.5 x ULN, then the liver fraction of Alkaline Phosphatase should be ≤ 2.5 x ULN
[a] Creatinine clearance should be calculated per institutional standard.	

6.2.7 Phase I component: Patients may have measurable or non-measurable disease.
Phase II component: Patients may only have measurable disease.

6.2.8 Patient must have no persistent toxicities from prior therapy ≥ Grade 2 with the exception of hematologic indices (i.e. hemoglobin, WBC, ANC, ALC).

6.2.9 For females of childbearing potential, a negative serum pregnancy test must be documented within 72 hours of receiving the first dose of vorinostat.

6.2.10 Patient, or the patient's legal representative, has voluntarily agreed to participate by giving written informed consent.

6.2.11 Female patients of childbearing potential must be willing to use 2 adequate barrier methods of contraception to prevent pregnancy or agree to abstain from heterosexual activity throughout the study, starting with visit 1.

6.2.12 Male patients must agree to use an adequate method of contraception for the duration of the study.

6.2.13 Prior Therapy: Patients must have fully recovered from the acute toxic effects of all prior chemotherapy, immunotherapy, or radiotherapy prior to entering this study.

Myelosuppressive chemotherapy: At least 2 weeks must have elapsed since the administration of previous therapy. Six weeks must have elapsed since administration of nitrosoureas or mitomycin C. Seven days must have elapsed since the administration of G-CSF and/or GM-CSF.

Biologic agents: At least 14 days must have elapsed since the completion of therapy with a biologic agent such as a monoclonal antibody. Seven days must have elapsed since the last dose of retinoids.

Radiation therapy (XRT): ≥ 2 weeks must have elapsed for local XRT (small port); ≥ 6 months must have elapsed if prior radiation to ≥ 50% of the pelvis or if other substantial bone marrow irradiation, including total body irradiation.

6.2.14 Patient must be able to swallow capsules.

6.2.15 Patient must have an available archival/pre-treatment block, or fresh tumor biopsy for molecular profiling to be performed (See section 10.8.2 of the protocol for specific requirements).

6.3 Subject Exclusion Criteria

A patient meeting any of the following criteria is not eligible to participate in this study:

6.3.1 Patients currently participating or has participated in a study with an investigational compound or device within 4 weeks of initial dosing with study drugs.

6.3.2 Patients with a prior history of treatment with HDAC inhibitors (e.g. SNDX-275/entinostat, LAQ-824, LBH589, PXD-101/belinostat, etc). Patients who have received Valproic acid will be excluded from this study.

6.3.3 Patients with non CNS primary tumors who have known brain metastases or symptomatic CNS disease (e.g. cranial nerve abnormalities) without cytologic abnormality in the CSF should be

excluded from this clinical trial because of their poor prognosis and known propensity for the development of progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events. Patients with metastatic CNS tumors will **not** be excluded from enrollment on this study in the phase I component only.

6.3.4 Patients who have undergone prior autologous stem cell transplantation or allogeneic transplantation.

6.3.5 Uncontrolled intercurrent illness or circumstances that could limit compliance with the study requirements including, but not limited to: ongoing or active bacterial or fungal infection, acute or chronic graft versus host disease, symptomatic congestive heart failure, cardiac arrhythmia, or psychiatric illness/social situations.

6.3.6 Patients who are pregnant or breastfeeding, or expecting to conceive within the projected duration of the study. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with vorinostat, lactating patients will be excluded from this study.

6.3.7 Patients known to be Human Immunodeficiency Virus (HIV)-positive.

6.3.8 Patients with known hypersensitivity to the components of the study drugs or their analogs.

6.3.9 Patients with symptomatic ascites or pleural effusion. A patient who is clinically stable following treatment for these conditions is eligible.

6.3.10 Patients who are at the time of signing informed consent, a regular user of any illicit drugs, substance abuser or who have a recent history of drug or alcohol abuse.

6.3.11 Patients with a known history of Hepatitis B or C.

6.3.12 Patients who have a history of gastrointestinal surgery or other procedures that might in the opinion of the investigator, interfere with the absorption or swallowing of the study drug.

6.3.13 Patients who are unable to take or tolerate oral medications on a continuous basis.

6.3.14 Patients with a history of a prior malignancy who have undergone potentially curative therapy with no evidence of that disease for five years, or patients who are deemed low risk for recurrence by his/her treating physician are permitted to enroll.

7.0 RECRUITMENT PLAN

7.1 Patients or their parent/legal guardian will be required to sign a statement of informed consent indicating the investigational nature of this study.

7.2 Qualified physicians who may seek consent for entry of patients on this study are listed in Section 15.1.

7.3 The informed consent will be signed and dated by the patient, parent or the patient's legally authorized representative and by the physician obtaining informed consent according to institutional guidelines. One copy will be given to the patient/parent/legal guardian to be retained for their personal records. One copy will be maintained on file at the POETIC DCC. The original document will be confidentially maintained by the participating institution.

7.4 A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the patient and/or his/her parents, to the degree of their understanding, acknowledge and accept the risk of participation in this study.

7.5 Written consent must be documented on the appropriate consent form approved by the local Institutional Review Board at each of the respective participating centers. Attainment of the written consent must be verified by the DCC prior to entry on study. A copy of the consent form, along with the eligibility checklist, and Health Insurance Portability and Accountability Agreement (HIPAA) must be submitted to the DCC prior to enrollment of any subject on this study. Verification of subject enrollment on this study is defined in section 15.0.

Every effort will be made to include women, children of both sexes, and minorities in the study population for this trial. No patient will be excluded from participation in this trial on the basis of gender, ethnicity, or race. Review of accrual to past pediatric multicenter studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. The small number of patients entered into this trial will obviate any analysis of variation in toxicity profile or response rate with gender or ethnicity.

Data from the institutions participating in this trial have been reviewed with respect to enrollment of patients of different races and genders. It is anticipated that enrollment of the current study will follow the same pattern.

Table 6

Institution	Number of New Patients/ Year	White Non-Hispanic (%)	Black Non-Hispanic (%)	Hispanic (%)	Other (%)
MSKCC	**147**	**61.0**	**19.0**	**15.0**	**5.0**
JHMC	**77**	**73.0**	**21.0**	**1.0**	**5.0**
UCD/TCH	**204**	**62.0**	**0.0**	**34.0**	**4.0**
MDACC	**146**	**60.0**	**5.0**	**29.0**	**6.0**
UF	**93**	**81.5**	**16.5**	**0.8**	**0.8**
PCH	**137**	**65.7**	**< 0.1**	**27.7**	**6.5**
All Children's	**100**	**63**	**19**	**15**	**2**
CMH	**184**	**71.0**	**12.0**	**13.0**	**4.0**
DFCI	**250**	**81.3**	**4.7**	**5**	**9.2**

8.0 PRETREATMENT/ENROLLMENT EVALUATIONS

Studies required for patients enrolled on this study are summarized in the table included in Section 10.1. The following studies will be performed for all patients. If the complete physical exam, laboratory evaluations and EKG are completed within 72 hours of receiving treatment in cycle 1, then cycle 1 week 1 evaluations do not need to be repeated.

8.1 A complete physical examination to be completed $\leq$ 7 days prior to start of protocol therapy and will include: vitals signs (HR, RR, BP, Temp, height, weight, and performance status), complete medical history, prior anti-cancer therapy, and medications given within 7 days prior to the start of protocol therapy.

8.2 Laboratory studies will be obtained $\leq$ 7 days prior to the start of protocol therapy and will include: complete blood count w/diff, PT/PTT (with INR), fibrinogen, LDH, albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose,

phosphorus, potassium, total protein, SGOT(AST), SGPT(ALT), and sodium. A serum pregnancy test will be obtained in all females of childbearing potential.

8.3 A serum pregnancy test will be obtained in all females of childbearing potential within 72 hours of receiving the first dose of vorinostat.

8.4 Pre-treatment samples for correlative studies conducted on peripheral blood and bone marrow specimens are described below in section 10.0

8.5 An EKG will be performed at baseline

8.6 An extent of disease evaluation should be performed to evaluate the primary tumor and sites of metastatic disease including radiologic studies appropriate for the disease (i.e. CT, MRI, PET, bone scan, chest x-ray, etc.) and must be done < 4 weeks prior to the start of therapy. PET imaging will be obtained as a correlative study in all patients for whom this imaging study is standard of care and who have PET capability at their sites. For these patients, it is recommended that a baseline PET scan be performed as part of the pre-treatment extent of disease evaluation and that the PET scan be repeated after the second cycle of treatment for the analysis. While these scans are recommended, they are not required for study entry.

8.7 In the event that the patient's condition is deteriorating due to disease progression, laboratory evaluations should be repeated within 48 hours prior to initiation of the first and all subsequent cycles of therapy

9.1 TREATMENT/INTERVENTION PLAN

9.2 Treatment Administration

Treatment may be administered on an inpatient or outpatient basis. Reported adverse events and potential risks for vorinostat and etoposide are described in Section 17.2. Appropriate dose modifications for vorinostat and etoposide are described in Section 9.13. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

9.3 Treatment Schema

The dosing schedule for this study will consist of a 21-day cycle. The study PI must be contacted in the event of scheduling conflicts due to holidays. Vorinostat will be administered orally on Days 1-4 of every cycle at a starting dose of 125 mg/m^2/dose. The starting dose of vorinostat will be 50% of the pediatric single agent RP2D for the oral formulation. The starting dose of vorinostat is approximately 70% of the dose that acceptable dose reported in combination with the biologic agent 13 cis-retinoic acid reported by Fouladi et al. The dose of Vorinostat will be escalated in increments of 30% as long as there is no evidence of dose limiting toxicity.

If dose limiting toxicity is demonstrated at the Dose level 1, the dose of Vorinostat will be reduced de-escalated by 25% (Dose Level -1). If a patient experiences emesis within 30 minutes of receiving vorinostat the dose should then be repeated.

Etoposide will be administered intravenously over 1 hour (+ 10 minutes) on Days 3-5 of every cycle at a fixed dose of 100 mg/m^2/dose in both phase I and II components of the study. See Schema in Table 7 below.

For initial onset of treatment, in both components of the study, the patient must meet the ANC criteria of ≥ 1000/mcL and a platelet criteria of ≥ 100,000/mcL as defined in section 6.1.6. For the second or greater courses of treatment, the hematologic criteria for initiation will be ANC ≥ 750/mcL and platelet count of ≥ 75,000/mcL.

Table 7

REGIMEN DESCRIPTION			
Agent	**Route**	**Schedule (per cycle)**	**Cycle Length**
Vorinostat	Po	Days 1-4	21 days
Etoposide	IV	Days 3-5	

9.4 Phase I Component: Dose Escalation

Inter-patient dose escalation will proceed as follows:

Table 8

DOSE ESCALATION SCHEDULE		
Dose Level	**Dose**	
	Etoposide (mg/m^2)	Vorinostat (mg/m^2)
-2	75	100
-1	100	100
1	100	125
2	100	160
3	100	210
4	100	270

The following dose rounding table should be used as a reference for drug dosing dispensed based upon body surface area:

Vorinostat Dose (mg/m^2)	**BSA**							
	0.5 – 0.74	**0.75 – 0.99**	**1 – 1.24**	**1.25 – 1.49**	**1.5 – 1.74**	**1.75-1.99**	**2 - 2.24**	**2.25-2.49**
100	100	100	100	100	200	200	200	200
125	100	100	100	200	200	200	300	300
160	100	100	200	200	200	300	300	400
210	100	200	200	300	300	400	400	500
270	200	200	300	400	400	500	500	600

Intra-patient dose escalation is not permitted. At the highest dose level below the MTD, if the equivalent of ≤1 out of 6 patients experiences DLT, then this dose will be the recommended Phase II dose (RP2D). At least 9 patients must be entered at the RP2D. Prior to proceeding to the Phase II component, the Principal Investigators of the study will review all clinical data with the sponsor before establishing the RP2D.

9.5 Phase II Component

In the phase II component, patients will be treated at the RP2D established in the Phase I component of the study, which was found to be 270 mg/m^2/dose of Vorinostat and 100 mg/m^2/dose of Etoposide. Evaluation for response will be determined by Revised RECIST guideline (version 1.1) [55] after every 2 cycles of therapy (> 4 and < 6 weeks from the start of the first cycle of treatment) as defined in section 12.0.

9.6 Vorinostat

9.6.1 Route of Administration

Vorinostat capsules will be administered on Days 1-4 of every cycle. Vorinostat must be administered exactly 4 hours prior to administration of Etoposide on Days 3 and 4 of therapy. All doses and administration times of vorinostat must be documented on the patient diary and/or the patient's medical record.

9.6.2 Diet

Vorinostat should be taken within approximately 30 minutes of a meal whenever possible. Altered taste and decreased food and liquid intake are associated with vorinostat administration. These toxicities can be actively managed with fluid management and nutritional consult.

During the period of vorinostat administration, patients should consume at least 2 liters or maintenance volume of fluids orally, each day, to prevent dehydration. Patient may require electrolyte replacement. If patients are experiencing dysgeusia, popsicles or Gatorade may be successful in maintaining oral intake. Early use of anti-emetics should be encouraged.

9.6 Etoposide

9.6.1 Route of Administration

Etoposide will be administered at a fixed dose of 100 mg/m^2/day intravenously over 1 hour (+ 10 minutes) for three consecutive days on Days 3-5 of therapy. Most pediatric patients with recurrent, refractory disease will have a central venous access device (CVAD) in place prior to entry onto this study and, when possible, the drug will be infused using the CVAD. In patients who do not have indwelling CVADs, etoposide will be administered via peripheral intravenous (IV) access. In the event of an anaphylactic reaction, the infusion of etoposide should be terminated. In the event of hypotension, the infusion of etoposide should be stopped and Normal Saline administered until the blood pressure normalizes. Once the blood pressure has normalized, the infusion may be re-instituted and the rate of administration decreased to double the interval of administration (2H). Source documentation for etoposide administration start and end times, and dose must be provided.

9.6.2 Etopophos

In the event of an anaphylactic reaction to Etoposide, Etopophos may be used in place of Etoposide. The dose and schedule of administration will be identical to that previously indicated for Etoposide in Section 9.2.

9.7 Definition of Dose-Limiting Toxicity

Toxicity will be evaluated according to NCI CTCAE Version 4.0. Any of the following events which are attributed to study therapy (i.e., considered possibly, probably, or certainly related to study therapy) will be considered DLTs. Only DLTs occurring in the first cycle will be considered in the determination of dose cohorts and the MTD. The period of observation for DLT will be 21 days from the first dose of study medications.

9.7.1 Definition of Hematologic Dose-Limiting Toxicity

9.7.1.1 Any Grade 4 hematologic toxicity including neutropenia and thrombocytopenia as indicated below:

- Febrile neutropenia defined as Grade 3 or 4 neutropenia with fever $\geq$ 38.5ºC and/or infection requiring antibiotic or antifungal treatment
- Any Grade 4 neutropenia lasting > 7 days
- Grade 4 thrombocytopenia lasting > 7 days
- Treatment delay for more than 21 days due to toxicity $\geq$ Grade 2
- Any drug-related adverse experience, regardless of grade, leading to a dose reduction of one or more study drugs.

9.7.2 Definition of non-hematologic Dose-Limiting Toxicity

9.7.2.1 Non-hematologic dose-limiting toxicity will be defined as any Grade 3, 4, or 5 nonhematologic toxicity, with the specific exception of:

- Grade 3 nausea or Grade 3 vomiting that in the opinion of the Investigator occurs in the setting of inadequate compliance with supportive care measures specified in Section 9.8.5 and lasts for less than 48 hours.
- Grade 3 diarrhea that in the opinion of the Investigator occurs in the setting of inadequate compliance with supportive care measures specified in Section 9.8.5 and lasts for less than 48 hours.
- Grade 3 dehydration that in the opinion of the Investigator occurs in the setting of inadequate compliance with supportive care measures specified in Section 9.8.5 and lasts for less than 48 hours.
- Alopecia
- Inadequately treated hypersensitivity reactions
- Grade 3 elevated transaminases of < 1 week in duration

9.7.3 In addition, the following will also be considered DLT:

- Any drug-related adverse experience, regardless of (CTCAE) version 4.0 grade, leading

to a dose modification of vorinostat;
- Unresolved drug-related toxicity, regardless of (CTCAE) version 4.0 grade, lasting for 3 weeks or more from the date of the last scheduled treatment;
- Requirement for dose reduction by two dose levels due to toxicity.

Dose escalation will be determined based on the occurrence of DLTs. For the purposes of deciding whether to advance the Dose Level, DLTs will be counted by patient (i.e., a patient who experiences more than 1 DLT will be counted only once).

Management and dose modifications associated with the above adverse events are outlined in Section 9.13.

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

Number of Patients with DLT at Given Dose Level	**Escalation Decision Rule**
0 of 3	Enter 3 patients at the next dose level.
≥2 of 3	Dose escalation will be stopped. This dose level will be declared the maximally administered dose (highest dose administered). Up to 3 additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
1 of 3	Enter at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose.
≤1 of 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at this dose.

9.8 General Concomitant Medications

The major pathways for metabolism of vorinostat involve glucuronidation and hydrolysis followed by ß-oxidation. Therefore, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs that are known to be CYP enzyme inhibitors. Formal drug-drug interaction studies have not been performed with vorinostat. All concomitant medications received within 7 days before the first dose of study medication and 30 days after the last dose of study medication must be recorded in the source document and on the case report form.

9.8.1 The Principal Investigator should be alerted if the patient is taking any over the counter medication or herbal supplements.

9.8.2 The concomitant use of other medications/therapies is allowed unless specifically prohibited in the protocol. Patients should be stabilized prior to study entry on all medications.

- Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) have been observed in patients receiving vorinostat concomitantly with coumarin derivative anticoagulants. Physicians should carefully monitor PT and INR in patients concurrently administered vorinostat and coumarin derivatives.

- Patients may not receive chemotherapy, radiotherapy, biological therapy or investigational anticancer therapy during the study. Patients who require these therapies should be considered to have progressive disease and be withdrawn from the study.
- Vorinostat should not be administered concomitantly with other HDAC inhibitors (e.g., valproic acid) as class-specific adverse reactions may be additive.

9.9 Supportive Care Guidelines

9.9.1 Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes, and general supportive care are to be used as clinically indicated. Diagnostic studies needed for good supportive care should be performed as clinically indicated. Patients who experience indigestion or gastroesophageal reflux symptoms on vorinostat may be treated with Proton Pump Inhibitors (PPIs) as well as H2 blockers as clinically indicated.

9.9.2 Growth factors are not to be used routinely in patients on this study. Administration of filgrastim in patients with serious neutropenic complications such as sepsis syndrome, fungal infection, etc. may be administered at the investigator's discretion. Use of filgrastim should be discussed with the Study Principal Investigator prior to its use, but should only be administered if clinically warranted.

9.9.3 Use of corticosteroids as anti-emetics is <u>contraindicated</u>.

9.9.4 There is no contraindication to administration of anti-emetics for the subjects.

9.9.5 Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Diarrhea:** Diarrhea should be treated promptly with appropriate supportive care, including administration of an anti-diarrheal agent according to standard practice guidelines for loperamide. The anti-diarrheal agent loperamide should not be taken prophylactically. Patients should be instructed to begin taking the anti-diarrheal agent loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. The daily dose of Loperamide should not exceed 16 mg/day. Loperamide should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Patients should also be advised to drink liberal quantities of clear fluids to help prevent dehydration.

- **Nausea/vomiting:** Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. In particular, the use of anti-emetics including 5HT3 antagonists and/or aprepitant is encouraged. Patients should be strongly encouraged to maintain liberal oral fluid intake during therapy, especially during the initial 14 days of each treatment cycle.

- **Anemia:** Transfusions may be used as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.

- **Neutropenia**: Prophylactic use of colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF should not be used during the first cycle of therapy. This must be discussed with the Study Principal Investigator prior to institution of this modality.

  Factors may be used if clinically indicated in subsequent cycles as outlined in the guidelines for dose modification. This must be discussed with the Study Principal Investigator.

- **Thrombocytopenia**: Transfusion of platelets may be used if clinically indicated in a manner consistent with the guidelines for dose modification.

- **Hyperglycemia:** Hyperglycemia has been observed in patients receiving vorinostat. Serum glucose should be monitored. Adjustment of diet and/or anti-hyperglycemic therapy may be necessary.

- **Electrolyte Disturbances**: Hypokalemia or hypomagnesemia should be corrected prior to administration of vorinostat, and consideration should be given to monitoring potassium and magnesium in symptomatic patients (e.g. patients with nausea, vomiting, diarrhea, fluid imbalance or cardiac symptoms.)

9.10 Duration of Therapy

In the absence of treatment delays due to adverse events and as long as the patient has optimal response (stable disease or greater), treatment may continue up to 1 year or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator
- Pregnancy

9.11 Duration of Follow Up

For patients removed from study due to disease progression or unacceptable toxicity, a follow-up period of 30 days from the last dose of protocol therapy will be required. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients that achieve an objective response will be followed every 3 months or until another treatment is administered.

9.12 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 9.7 and 13.0 apply. The reason for study removal and the date the patient was removed must be documented on the Case Report Form

9.13 Dosing Delays/Dose Modifications

Therapy will be held for patients who experience ≥ grade 3 non-hematologic toxicities related to therapy until resolution or return to baseline. If dosing is delayed >3 weeks, the patient will be removed from study.

9.13.1 Dose Modification Plan **(Phase I Component only)**

Patients who experience a DLT may be retreated with doses of vorinostat reduced by one level for a maximum of 2 dose level reductions. There will be no dose re-escalations. All toxicity from the higher dose level must have resolved prior to re-treatment at a lower dose level. Patients who respond to therapy but experience a DLT may continue to receive vorinostat at a lower dose level until intolerable toxicity is encountered or until the patient experiences progressive disease regardless of the duration of treatment.

9.13.2 Dose Modification for Toxicity Not Considered to be DLT **(Phase I Component only)**

Following the occurrence of any Grade 3 toxicity with the exception of neutropenia, thrombocytopenia, leukopenia, lymphopenia and anemia that does not constitute a DLT, vorinostat will be held until there is resolution to ≤ Grade 1 or return to baseline. Patients whose treatment is re-started after a dose delay for transient toxicity will continue at the original dose and frequency. In this manner, the whole schedule will be moved forward in time but the interval between subsequent doses will not change. Thus, in the absence of disease progression or DLT, the effect of schedule interruption will be to reduce the dose intensity without reducing the total dose. If dosing is delayed for > 3 weeks, the patient will be removed from the study.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

Studies required for patients enrolled on this study are summarized in the table below. The following studies will be performed in all patients. Cycle 1, week 1 complete physical exam, laboratory evaluations and EKG evaluations do not need to be repeated if completed within 72 hours of treatment.

10.1 A complete physical examination to be completed weekly and as clinically indicated, to include: vitals (HR, RR, BP, Temp), and all current medications will be documented.

10.2 Height, weight, BSA, and performance status will be collected at the beginning of each cycle

prior to receiving treatment.

10.3 The following laboratory studies will be obtained weekly: complete blood count w/diff, PT/PTT (with INR), fibrinogen, LDH, chemistry panel including the following components: albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT(AST), SGPT(ALT), and sodium.

10.4 Post-treatment samples for correlative studies conducted on peripheral blood and bone marrow specimens are described below.

10.5 An EKG will be performed prior to every cycle of therapy. If the EKG is performed within 72 hours of starting each cycle, then a repeat EKG does not need to be performed.

10.6 An extent of disease evaluation should be performed to assess the primary tumor and sites of metastatic disease including radiologic studies appropriate for the disease (i.e. CT, MRI, PET, bone scan, chest x-ray, etc.) as defined in section 12.0.

Disease assessment must be completed at a POETIC institution. For collaborating non-POETIC institutions, the reviews may be done by an institutional radiologist. PET imaging will be obtained as a correlative study in all patients for whom this imaging study is standard of care and who have PET capability at their site. For these patients, it is recommended that a baseline PET scan be performed as part of the pre-treatment extent of disease evaluation and that the PET scan be repeated after the second cycle of treatment for this analysis. While these scans are recommended, they are not required for study entry.

10.7 In the event that a patient's condition is deteriorating due to disease progression, laboratory evaluations should be repeated within 48 hours prior to initiation of the first and all subsequent cycles of therapy.

REQUIRED OBSERVATIONS

	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10 (Every 3 weeks)	Final Visit
Vorinostat[a]		X			X			X			X	
Etoposide[b]		X			X			X			X	
Informed consent	X											
Demographics	X											
Medical history	X											
Concurrent meds	X	X----------									----------X	X
Physical exam	X	X	X	X	X	X	X	X	X	X	X (weekly)	X
Vital signs (HR, RR, BP, Temp)[i]	X	X	X	X	X	X	X	X	X	X	X (weekly)	X
Height, Weight, BSA, Performance status[i]	X	X			X			X			X	X
CBC w/diff, Fibrinogen, PT/PTT/PT(INR)[i]	X	X	X	X	X	X	X	X	X	X	X	X
Serum/Plasma chemistry[c, i]	X	X	X	X	X	X	X	X	X	X	X	X
EKG[g]	X	X			X			X			X	X
B-HCG[d]	X											
Adverse event evaluation	X	X----------									----------X	X
Radiologic evaluations/ Tumor measurements	X					Tumor measurements are repeated > 4 and < 6 from the start of the first cycle of Documentation (radiologic) must be provided for patients removed from study for progressive disease.						X[e]
MSAS (for ages 10-18) optional	X					MSAS is to be completed between > 4 and < 6 weeks from the start of the first cycle of treatment						
PET scan (if applicable to disease) optional[h]	X					Radiologic measurements should be performed > 4 and < 6 weeks after the 1st 2 cycles then every 6 weeks.						X[e]
Archival tissue or fresh tissue biopsy for expression profiling (required)[f]	X	X										
Blood and/or Bone marrow for expression profiling (optional)[f]	X	X										
Histone Phosphorylation Profiling (optional)[f]	X	X										
Blood and/or Bone marrow for Histone Acetylation (optional)[f]	X	X										

a: Vorinostat: Dose as assigned; Po Days 1-4 of every 21 day cycle (Vorinostat to precede Etoposide exactly 4 H on the day of administration of Etoposide)
b: Etoposide: Dose as assigned; IV Days 3-5 of every 21 day cycle
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
d: Serum pregnancy test (women of childbearing potential)
e: Final visit evaluations
f: Collection procedures for the pre study and 24 hour collection for Histone expression profiling, Histone acetylation, Histone phosphorylation profiling are described in Section 10.8 and in Appendices II; III; VII
g: If baseline EKG is performed within 72 hours of starting treatment, then the Cycle 1 EKG does not need to be performed. This may apply for all subsequent cycles prior to treatment with vorinostat.
h: The PET scans taken for regular radiologic disease evaluation at baseline and Cycle 2 will also be used for the correlative study component.
i: If the baseline assessment is completed with 72 hours of starting treatment, then cycle 1, week 1 assessment does not need to be performed.

Evaluations in patients who experience treatment delays

In the event of a treatment delay, the timetable for the evaluations above will be modified so that studies are performed at the times appropriate relevant to drug administration. Height, weight, vital signs, and performance status will be checked and documented during weeks in which drug is administered. The body surface area will be re-calculated every cycle and the dose adjusted if there is a 10% change in body weight. Physical examinations will also be performed and documented during weeks in which drug is administered. Laboratory studies as shown in the table will be performed on a weekly basis during weeks in which drug is administered and during the following weeks. In the event of treatment delay, laboratory studies will be performed at additional time-points as needed for good patient care. Radiographic assessments will be performed after every 2 cycles of therapy.

10.8 Correlative/Exploratory Studies

The study will incorporate biologic correlative studies to evaluate the following: histone acetylation, gene expression profiling, and histone phosphorylation profiling. It is hoped that incorporation of these correlative studies will enhance our understanding of histone deacetylation in pediatric patients with refractory solid tumors treated with the proposed novel combination, vorinostat and etoposide. All correlative studies are optional, but are strongly encouraged to be collected.

10.8.1 Histone Acetylation

The processing of the peripheral blood and if possible bone marrow samples from patients with > 25% tumor involvement will be carried out in the laboratory of Dr. Robert Arceci at Ron Matricaria Institute of Molecular Medicine at Phoenix Children's Hospital, an expert in the molecular pharmacology of histone acetylation. Dr. Arceci has an experienced laboratory for analysis of histone acetylation and was a critical collaborator in the development of vorinostat. Processing the samples at Dr. Arceci's lab will ensure consistent sample handling and high quality data. Collection of blood and bone marrow is an important part of this study and whenever possible should be collected at the time points indicated below.

Sample Collection Time Points

Five mL of peripheral blood and five mL of bone marrow aspirate specimen if indicated (bone marrow with > 25% tumor involvement), will be obtained in a sodium heparin tube prior to treatment with Vorinostat and Etoposide and 24 H following the first dose of vorinostat if consent for this procedure is obtained.

Sample Collection Procedure and Handling

Phase I Component: For the first six patients enrolled on trial, the blood will be collected and handled in the following manner. One sample of peripheral blood will be collected, submitted, and shipped immediately without processing to the laboratory listed below. The second sample with be processed Ficoll Hypaque and flash frozen then shipped to the lab listed below (See Appendix VIII for Ficoll Hypaque process for whole blood).

Phase II Component: All patients in the phase II component of the trial, blood will be collected and handled in the following manner. One sample of peripheral blood and bone marrow if indicated (bone marrow with > 25% tumor involvement) will be collected without processing and shipped immediately to the laboratory listed below. These samples are to be collected prior to receiving treatment and 24 hours following the first dose of vorinostat.

Samples should be obtained and shipped Monday through Thursday via overnight delivery to:

Robert J. Arceci, M.D, PhD
C/O David Lee
Department of Child Health
University of Arizona, College of Medicine-Phoenix
Ron Matricaria Institute of Molecular Medicine
At Phoenix Children's Hospital
445 N. 5th Street
TGen Building, 3rd Fl, Room 322
Phoenix, AZ 85004
Phone: 602-933-0920
Fax: 602-933-0276
E-mail: rarceci@phoenixchildrens.com

10.7.1 Gene Expression Profiling

The processing of archival tumor or fresh tissue biopsy (if available), and peripheral blood samples (including bone marrow if > 25% tumor involvement) for gene expression profiling of will be carried according to established procedures. These samples will be shipped to Dr. Aru Narendran at the address listed below, but the processing will be carried out by Dr. Olga Kovalchuk at the University of Lethbridge to ensure consistent sample handling and high quality gene expression data. Collection of peripheral blood (including bone marrow if > 25% tumor involvement), and archival tumor or fresh tissue biopsy (if available) samples for expression profiling is an important part of this study and will be collected at the time points indicated below.

To ensure that these samples are obtained at the correct time, the vorinostat dose will be administered in the clinic on Cycle 1only. The time of the vorinostat dose and sample collection must be recorded. Refer to Appendix II for detailed methodology. Refer to Appendix II for the detailed sample collection procedure for peripheral blood.

Sample Collection Time Points

Formalin-Fixed Paraffin-Embedded Tissue and RNAlater™ Preserved Tumor Biopsy (Required)

It is required that patients have archival tumor samples available. Archival tumor samples may be from original diagnosis and/or any subsequent biopsy material. Whole formalin-fixed paraffin embedded tissue from patient's original diagnosis and/or any subsequent biopsy material tissue must contain a tumor specimen measuring at least 0.5cm x 0.5cm x 100 microns. If the blocks cannot be sent to for sectioning, then sections from the blocks will be accepted. At least six sections measuring 10 microns and ten sections measuring 4 – 5 microns should be provided.

Fresh Tissue Biopsy

For patients that do not have an archival tissue or prior biopsy available, a fresh tissue biopsy may be obtained in patients who have an accessible site for biopsy and for whom informed consent is obtained for this procedure. These samples will be obtained prior to treatment with vorinostat and 24 hours following the first dose of Vorinostat. These samples must be immediately placed in a 5 mL cryovial containing RNAlater™ after collection

Peripheral Blood and Bone Marrow (If > 25% tumor involvement)

The pre-treatment and on-treatment blood samples (2.5 mL each) will be collected in a PAXgeneTM RNA collection tube (2 tubes per patient) in all patients. The on-treatment samples will be collected 24 hours following the first dose of vorinostat.

Samples should be obtained and shipped Monday through Wednesday via overnight delivery to:

Dr. Aru Narendran
Alberta Cancer Research Institute
HRIC Lab 2a34
3280 Hospital Drive NW
Calgary, Alberta
T2N 4Z6
CANADA
Tel: (403) 210-6402
E-mail: anarendr@ucalgary.ca

10.7.3 Histone Phosphorylation Profiling

Previous studies have shown that the effects of HDAC inhibitors can be detected in peripheral mononuclear cells. In this study, we plan to evaluate phosphorylation profiling using antibody arrays to provide target identification and target validation data to monitor the effectiveness of vorinostat. The rationale for this approach and the methodology to be used are described in Appendix III. The analysis will be conducted in peripheral blood mononuclear cells in Cycle 1 only prior to vorinostat and 24 H following the first dose of vorinostat. These studies will be conducted in the laboratory of Aru Narendran MD, PhD at Alberta Cancer Research Institute. The address is listed below:

If patients/guardians give appropriate consent**,** peripheral blood (2.5 mL) will be collected as described in Appendix II. Samples should be obtained and shipped Monday through Wednesday via overnight delivery to:

Dr. Aru Narendran

Alberta Cancer Research Institute
HRIC Lab 2a34
3280 Hospital Drive NW
Calgary, Alberta
T2N 4Z6
CANADA
Tel: (403) 210-6402
E-mail: anarendr@ucalgary.ca

Refer to Appendix III for detailed methodology.

10.7.4 Positron Emission Tomography (PET)

Positron emission tomography (PET) will be incorporated into this trial as a correlative study in patients with solid tumors to obtain exploratory data about response assessment using this imaging modality in pediatric patients. PET is a diagnostic imaging tool that evaluates *in vivo* biologic changes using radiopharmaceuticals that mimic endogenous molecules. Accuracy of tumor assessment has been enhanced significantly by using ^{18}F-fluorodeoxyglucose ([^{18}F]FDG) PET for dynamic imaging of response to a variety of regimens used for treatment of adult tumors. There is a paucity of data regarding functional imaging in pediatric patients. A secondary objective of this study will be to evaluate accumulation prior to and during treatment with vorinostat and etoposide in pediatric patient with solid malignancies.

PET/CT scans will be done at institutions with the capability to perform this imaging study. The PET/CT component of this study is not required for enrollment of patients with solid tumors. Solid tumors will be imaged with PET/CT at baseline and following completion of the second cycle of therapy.

The results will be compared to baseline PET/CT results. The probability of disease progression over time among patients with reduction in the [^{18}F]FDG standardized uptake value (SUV) of 60% or greater will be estimated using the method of Kaplan-Meier. PET results will not be used for assessment of response according to RECIST criteria but will be used to achieve the secondary study objective to correlate alterations in accumulation of [^{18}F]FDG with tumor response.

The protocol for PET/CT imaging is summarized as follows: Prior to PET/CT scanning, patients will fast for 6 hours (except for water). A whole body PET/CT scan will be carried out per institutional protocol for whole body evaluation of extent of disease after 15 mCi/1.73 m2 [^{18}F]FDG. Patients will be scanned 60 minutes after FDG injection. Imaging will commence immediately after the patient has voided. Whole body attenuation corrected images will be obtained per protocol.

A diagnostic CT scan will be carried out prior to acquisition of the emission PET images. There is no breath hold for the CT component. Emission scans are typically carried out from the base of the skull to the mid-thigh. About 3 minute acquisition is carried out per field of view (~15 cm).

Studies are reconstructed using iterative reconstruction and using the non-contrast CT for attenuation correction. Attenuation-corrected PET images are visualized concurrently with the CT component. For the purpose of this trial, interpreters will not be blinded as to clinical or disease state parameters. Studies carried out at baseline (before treatment) and after 2 cycles of treatment with Vorinostat and Etoposide

will be comparable especially with respect to time after injection, camera used, and emission and CT acquisition parameters. A standardized uptake value (SUV), a semi-quantitative measure of tumor uptake of the [^{18}F]FDG adjusted for injected dose and body weight, will be calculated for each lesion. The method for calculating tumor uptake is by a differential uptake ratio of FDG in the tumor. It is defined as the ratio of the activity per gram within the lesion to the activity per gram if the activity were uniformly distributed through the whole patient. See equation below.

$$\text{SUV} = \frac{\text{activity/gram (lesion)}}{\text{activity injected/body weight}}$$

The SUV is obtained from the PET scanner directly for any region drawn on a PET scan image. In more depth, the numerator in the above equation is obtained from a region drawn around the lesion on one of the PET slices. The PET scanner is calibrated in units of activity per unit volume, and therefore this number is obtained automatically. This calibration is performed by medical physics, using a cylinder of water into which an exactly known amount of FDG has been added. A PET scan of this cylinder is used to determine a calibration factor which converts the counts from the PET scanner directly into activity per unit volume. The denominator is the activity injected into the patient divided by the patient weight. These numbers are entered into the PET scanner computer by the technologist. Hence the scanner is already calibrated to provide SUVs. SUV is a semi-quantitative measure of selective tracer uptake within lesions that is independent of the PET scanner upon which it is performed and therefore does not vary from center to center.

Interpretation of changes will follow visual scores (0: no uptake; 1: uptake equal to soft tissue; 2: uptake greater than soft tissue, equal to liver; 3: uptake greater than liver) and standardized uptake value (SUV), which will be normalized both to overall patient weight and to body surface area.

10.8.5 Exploratory Studies (MSAS)

Please refer to section(s) 3.6 and 4.5 of the protocol.

11.0 TOXICITIES/SIDE EFFECTS

Refer to Section 17.2

12.1 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Response in patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients with solid tumors should be reevaluated every 2 cycles ($\geq$ 4 and < 6 weeks from the start of the first cycle of treatment). In addition to a baseline scan, confirmatory scans will also be obtained 3 weeks following initial documentation of an objective response. If a durable response is documented, response will be re-assessed every 6 weeks.

12.2 Definitions of Response in Patients with Solid Tumors

Response and progression will be evaluated in this study using the international criteria proposed by the Revised RECIST guideline (version 1.1).[55] Changes in only the largest diameter (unidimensional

measurement) of the tumor lesions are used in the RECIST guideline. Note: Lesions are either measurable or non-measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

12.2.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm.)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest X-ray.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

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

12.2.2 Non-measurable Disease

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/ abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

12.2.3 Target Lesions

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

12.2.4 Non-target Lesions

All other lesions (or sites of disease) should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each

should be noted throughout follow-up, in rare instances unequivocal progression can be used. It is possible to record multiple non- target lesions involving the same organ as single item (e.g. multiple pelvic lesions).

12.3 Guidelines for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. Tumors in a previously irradiated area will be considered measurable.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and $\geq$ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are

initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

12.4 Response Criteria for Patients with Solid Tumors

12.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression)

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

12.4.2 Evaluation of Non-target Lesions

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

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

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. (Note: the

appearance of the one or more new lesions is also considered progression.)

Although a clear progression of "non-target" lesions only is exceptional, in such circumstances the opinion of the treating physician should prevail, and the progression status should be confirmed at a later time by the Study Principal Investigator.

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

12.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until the end of treatment taking into account any requirement for confirmation. The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria (Section 12.3 and Section 12.4)

Target Lesions	Non-target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note:

Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the

evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) before confirming the complete response status.

12.5 Confirmatory Measurement/Duration of Response for Patients with Solid Tumors

12.5.1 Confirmation

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments obtained 3 weeks after the criteria for response are first met. In the case of SD, follow-up measurements must meet the SD criteria at least once after study entry at a minimum interval of 6 weeks.

12.5.2 Duration of Overall Response

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

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

12.5.3 Duration of Stable Disease

Stable disease is measured from the start of the treatment until the criteria for progression are met, utilizing as reference the smallest measurements recorded since the treatment started.

13.1 CRITERIA FOR REMOVAL FROM STUDY

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from the study
- General or specific changes in the patient's condition that render the patient unacceptable for further treatment in the judgment of the investigator
- Pregnancy

The Study Principal Investigator must be notified if a patient is taken off study. The specific reason for discontinuation of therapy will be noted on case report forms (CRFs).

14.1 BIOSTATISTICS

14.2 Study Design/Endpoints

14.2.1 Phase I Component

This trial is a Phase I evaluation of vorinostat and etoposide with the starting dose and schedule as described in Section 9.3 The primary study endpoints will be assessment of toxicity based upon the determination of toxicity profile of the combination and determination of the MTD, DLT, and RP2D. A

minimum of 2 evaluable patients will be entered at each dose level. Patients will be evaluated for toxicity within the first cycle (3 weeks) of therapy. Dose escalation will not be considered until at least 3 patients at a given dose level have completed one course of therapy (e.g. 3 weeks) without a DLT. If a patient does not experience a DLT as defined in Section 9.7 but is taken off study due to unacceptable adverse events/toxicity, that patient will be considered to have had a DLT for the purposes of dose escalation. If therapy is discontinued during the first cycle for reasons other than toxicity, an additional patient may be enrolled at the dose level of the off-study patient to ensure adequate evaluation of toxicity.

The following design will be used to determine the MTD. Patients will be treated in cohorts of size 3 and 6 and the dosage will be escalated if the clinical toxicity is acceptable. The design is constructed to reduce the chance of escalating the dose when the probability of DLT is high, an increase the chance of escalating the dose when the probability of DLT is low. The MTD is defined as the highest dose level with an observed incidence of DLT in no more than 1 out of 6 patients treated at a particular dose level. The dose escalation scheme is as follows:

1) If none of initial 3 patients at a given dose level experience DLT, the next dose level is studied in another cohort of 3 patients.

2) If 1 of the initial 3 patients at a given dose level experience DLT, up to 3 additional patients will be treated at that same dose level. Escalation will continue if one of the six patients experience DLT.

3) If two or three patients experience DLT in the first three patients, or two or more patients experience DLT in six patients at a given dose level, the MTD will be determined as the preceding dose level.

4) If three or fewer patients are treated at a dose under consideration as the MTD, additional patients to total six will be treated at that level to confirm the MTD.

The dose escalation scheme provides the following probabilities of escalation based on the true chances of DLT at a specific dose level. One can see that the probability of escalation is high if the toxicity risks are low.

True Probability of Toxicity:	.10	.20	.30	.40	.50	.60
Probability of Escalation:	.91	.71	.49	.31	.17	.08

When the MTD is reached, the additional cohort of 3 patients will be recruited at this dose to allow for greater confidence in estimating the toxicity rate in this patient population (RP2D). If none of the 9 patients treated at the MTD experience a DLT, then we are 90% confident that the probability of a toxic event in this patient population is less than 0.23. However, if 3 or more DLTs are observed, the approximate 95% lower confidence bound on the probability of a DLT is 0.12, indicating unacceptable toxicity. If 3 or more DLTs occur in 9 patients, we will recommend the next lower dose level for further evaluation of this therapy, which would then be the recommended Phase II dose. This trial will require a

minimum of 2 patients. The maximum number of patients needed depends on the dose level reached. An interim safety analysis of the data in the Phase I component will be completed prior to starting the Phase II component. Although not a primary objective of this portion of the study, proportion of patients with response will be calculated.

14.2.2 Phase II Component

The primary endpoint of this component will be to evaluate the efficacy of the novel combination, vorinostat and etoposide, in the treatment of recurrent or refractory childhood malignancies with recurrent or refractory sarcoma. Efficacy is defined as a binary endpoint (CR+PR versus neither) after 2 cycles of treatment. We will use a minimax Simon two-stage design. Treatment of pediatric solid tumors with etoposide only results in approximately 20% response rate, however the disease type specific response rates are variable (osteosarcoma 9%, soft tissue sarcoma 8%, rhabdomyosarcoma 19%, and Ewing's sarcoma 40%). These 4 disease groups account for 20-30%, 10-20%, 30% and 30% of pediatric sarcomas respectively. Due to highly variable response rates and possible variability in number of recruited patients with specific sarcoma type, we have chosen an unpromising overall response rate to be 15%. The promising response rate is 35%. Initially we will recruit 15 patients. If there are 2 or fewer responses, the trial will terminate and the combination therapy will be deemed unpromising. If there are 3 or more responses among 15, enrollment will be extended to 28 patients. If 8 or more responses are observed among 28 patients, the trial will be considered to have a positive result. If there are 7 or fewer responses, the combination therapy will be considered unpromising for further study. The design allows early termination of the study due to inefficacy. The probability of early termination is 60% if the true treatment response is 15%. This design will effectively discriminate between true response rates of <15% and >35% with a type I error of 5% and power of 80%. Upon the completion of the study, the true response rate will be estimated as an observed rate, and the exact confidence interval will be constructed. Response rate within different sarcoma types will also be calculated.

14.3 Sample Size/Accrual Rate

14.3.1 Phase I Component

Review of data from the participating institutions regarding numbers of relapsed patients as well as accrual to Phase I studies indicates that 2-3 patients per month may be accrued. It is anticipated that 18-25 patients will be accrued. This will permit completion of the study within 1 year. Upon completion of the phase I component, an interim safety analysis will be performed before determination of the recommended Phase II dose of the combination.

14.3.2 Phase II Component

Review of data from the participating institutions regarding numbers of relapsed patients as well as accrual to Phase I studies indicates that 2-3 patients per month may be accrued. It is anticipated approximately 28 patients will be accrued. This will permit completion of the study within 1 year

14.4 Correlative Analysis

This study will incorporate biologic correlative analyses conducted in the phase I and II setting to evaluate the following: histone acetylation, gene expression profiling and cellular phosphorylation profiling. These markers will be correlated with tumor response and clinical characteristics using Wilcoxon rank sum test for continuous variables and Fisher exact test for binary variables. Descriptive statistics will be used to summarize the data at different time points.

A standardized uptake value (SUV), a semi-quantitative measure of tumor uptake of the [^{18}F]FDG adjusted for injected dose and body weight, will be calculated for each lesion using PET scan. The association of SUV with tumor response will be tested using Wilcoxon rank sum test.

14.5 Exploratory Analysis of symptom distress survey

It is expected that ¾ of all patients will be of the age 10-18 and will participate in the MSAS exploratory studies. The Statistical Package for the Social Sciences (SPSS, Version 17 for Windows) will be used to analyze the data regarding symptom distress. To test the research question in this study, the total MSAS scores and their subscales will be used. Descriptive statistics like mean, median and inter-quartile range will be calculated and compared across time. All variables will be examined for outliers through frequency distributions, measures of central tendency and skewness. Although comparisons will be made at each time point, the primary time points for evaluation are at baseline and at the time of the first three radiographic evaluations. Intraclass correlation (ICC) of the MSAS will be used to calculate the test.

15.1 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.2 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain written informed consent, by following procedures defined in Section 18.0, Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All patients must be centrally registered at the POETIC Data and Coordinating Center (DCC) located at Memorial Sloan-Kettering Cancer Center. Registrations will be handled by the Research Study Assistant (RSA) at the POETIC DCC. The contact telephone number is (646) 888-5714/5715 and the fax number is (646) 888-5726. Registrations will occur between 9:00 am and 5:00 pm Eastern Standard Time (EST), Monday through Friday and will include review of the signed consent form, HIPAA research authorization form, eligibility checklist, and eligibility source documentation. The RSA will also verify, via a FAX/email copy, that the written informed consent is obtained and dated prior to subject entry on the study.

The participating site must contact the RSA at the POETIC DCC to reserve a slot on the protocol when a patient is being considered for a trial. To begin a registration, the participating site must fax/email the signed consent form and HIPAA research authorization to the RSA within 48 hours of the patient signing consent. To complete the registration, the completed eligibility checklist, and eligibility source

documentation must be sent to the RSA at the DCC via fax/email prior to protocol treatment or any research tests.

All research participants are registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center by the DCC RSA. PPR is available Monday through Friday from 8:30 am - 5:30 pm. Registrations must be sent to the POETIC DCC and the RSA at MSKCC will verify eligibility and complete the registration with the PPR Office. Registration documents must be sent directly to the DCC prior to 4:00 PM to ensure timely processing, so that enough time is allowed for source verification. If a registration is sent to the DCC after 4:00PM, all efforts will be made to have the patient registered that day, but it cannot be guaranteed that a patient will be registered that day.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

Written consent must be documented on the appropriate consent form and Research Authorization designated and approved by the Institutional Review Board at the institution at which the patient is enrolled. The following Principal Investigators or their designated Co-Investigators may obtain informed consent:

Tanya Trippett, MD
Patrick Brown, MD
Jessica Boklan, MD
Lia Gore, MD
Cynthia Herzog, MD
Suzanne Shusterman, MD
Lisa McGregor, MD,PhD
Tony Truong, MD
Gregory Hale, MD
Kathleen Neville, MD
Amy Smith, MD

15.2Randomization

This study does not include randomization.

16.1 DATA MANAGEMENT ISSUES

16.2 Data and Coordinating Center (DCC)

The Research Study Assistant (RSA) at the POETIC DCC will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problems and prioritization. The Clinical Research Coordinator, (CRC) is responsible for coordination between the RSA and Research Staff at the following member institutions: All Children's Hospital, MD Anderson Cancer Center, Phoenix Children's Hospital, Sidney Kimmel Cancer Center (Johns Hopkins Medical Center), Alberta Children's Hospital, Children's Hospital Colorado, Pennsylvania State University College of Medicine, Dana-Farber Cancer Institute,

Children's Mercy Hospital & Clinics and Arnold Palmer Hospital for Children/ MD Anderson Cancer Center Orlando. The CRC at the POETIC DCC will also serve as the liaison among all staff involved including the principal investigators, attending physicians, and nurses.

Case report forms (CRFs) will be drafted in a standard format and will be provided to each participating institution by the DCC. Required study tools for each protocol including correlative studies, vital signs, drug administration and protocol evaluations will also be provided to each participating institution by the DCC. The participating Site PI is responsible for ensuring these forms are completed accurately and legibly. The Site PI is also responsible for ensuring that all CRFs, study tools, and corresponding source documentation are to the DCC one week after the completion of each cycle.

The data collected for this study will be entered into a secure database by the RSA at the POETIC DCC. Data will be collected, stored, and monitored at an institutional level via the Clinical Research Database (CRDB) system. Data will be provided from CRDB to protocol-defined sponsors (CTEP, FDA, etc.) as required, through the Data Management Resource Division, a division of the Office of Clinical Research.

Source documentation will be available to support the computerized patient record and must be submitted with the case report forms and required study tools. Case report forms will not be considered source documentation.

- Variables that will be recorded include the patient's birth date, date of diagnosis, date of study entry and histologic diagnosis.
- The results of the pretreatment and end of therapy evaluations, including the extent of disease evaluation (history, physical examination and imaging studies), baseline laboratory values, renal and hepatic function, as defined per protocol, will be recorded.
- All study related treatment data and concomitant drugs will be recorded.
- The presence of toxicity at baseline, during and for 30 days after administration of the investigational agent will be monitored and recorded.
- The results of the extent of disease evaluation (history, physical examination and imaging studies) following each course of treatment will be recorded.
- The patient's disease status and last follow-up will be recorded. If disease progresses or recurs, the results of the repeat extent of disease evaluation will be recorded.

16.3 Site Research Staff

Research staff will be assigned at All Children's Hospital, MD Anderson Cancer Center, Phoenix Children's Hospital, Sidney Kimmel Cancer Center (Johns Hopkins Medical Center), Alberta Children's Hospital, Children's Hospital Colorado, Pennsylvania State University College of Medicine, Dana-Farber Cancer Institute, Children's Mercy Hospital & Clinics and Arnold Palmer Hospital for Children/ MD Anderson Cancer Center Orlando. Their responsibilities will include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problems and prioritization, maintaining file documentation of data for the clinical trial, pharmacokinetic or other biologic correlative study collection, and analysis as outlined for each patient enrolled on study. They will also be responsible for maintaining a regulatory binder for each protocol. The designated research staff will also

be responsible for submitting the data on a weekly basis by fax or mail to the RSA at the DCC. Case report forms and required study tools along with supporting source documentation should be faxed/emailed or mailed to the address below, one week after the completion of each study cycle:

POETIC Data and Coordinating Center
Memorial Sloan-Kettering Cancer Center
405 Lexington Avenue, Rm 3-512
New York, NY 10174
Telephone: 646-888-5714/5715
FAX: 646-888-5726

16.4 Administrative Support

The protocol will be conducted as a single research study effort and data from each participating institution will be included in the analysis of results.

The Study Principal Investigator will be responsible for the conduct of the study, the monitoring of the progress of the study, and review of all case report forms from each participating institution.

Failure to submit required forms in the timelines requested will result in suspension of accrual privileges at a given site until data is updated, and/or withholding of contract payments if applicable.

Initial Protocol Submission

Prior to implementing this protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC IRB/PB. Prior to implementing this protocol at the participating centers, approval must be obtained from the participating center's Local IRB of Record. The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Local IRB of Record approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Local IRB of Record membership
- Local IRB of Record's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification and HIPAA training for investigators and key staff members
- Signed and dated FDA Related Forms 1572/1571 (if applicable)
- Lab Certifications and Reference Ranges for each lab listed on the 1572
- Appropriate financial disclosure forms.

Protocol Amendments/Status Changes

Each change to the protocol must be organized and documented by the POETIC DCC. After IRB approval at the lead institution, the POETIC DCC will distribute the amendment to the participating institutions, for submission to their local IRB within 60 days of the amendment date. The participating

sites will ensure that documentation for all IRB approved amendments are sent to the DCC and are maintained in the regulatory binder. This documentation will include the IRB approval letter referencing the protocol version date and amendment number, IRB approved protocol, IRB approved appendices and IRB approved consent forms.

The amendment will be written so that no other institution will need to reformat the information but can simply copy and distribute. An amendment memo as well as highlighted and clean copies of the protocol, appendices and consent forms will be distributed to the participating sites. The consent form will be a sample which may be edited in order to adhere to local IRB guidelines. The amendment must be submitted at each site to the IRB for review and approval before patients can be enrolled on the study and within 60 days of the amendment version date. The amendment number and version date will also be displayed on each amendment.

16.5 Additional IRB Correspondence

Annual re-approval

Annual re-approval from the participating center's Local IRB of Record must be submitted to the DCC at the time re-approval is granted. The most current approved version of the consent form should also be submitted to MSKCC at that time. Failure to submit the re-approval will result in suspension of accrual privileges.

Deviations and Violations

All deviations should be discussed with the Study Principal Investigator prior to submission to the Local IRB of Record. Deviation requests and approvals will then be forwarded to the DCC.

For protocol violations, the participating site should report to the violation to Dr. Tanya Trippett, the Director of the POETIC DCC, as soon as possible. Dr. Trippett will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to the Local IRB of Record as they occur, per institutional standards. Approvals/acknowledgments from the Local IRB of Record for protocol deviations and violations should be submitted to POETIC DCC as received.

Other correspondence

Participating sites should submit other correspondence to their local IRB of Record according to local guidelines, and submit copies of that correspondence to MSKCC.

16.6 Quality Assurance

Quality assurance is a central responsibility of the POETIC DCC and it will be achieved by frequent review, constant oversight, and input from objective advisors. Each project will maintain a steering committee which will meet in conference call on a weekly basis to critically review the scientific progress of the clinical trial. The steering committee will include the principal investigators, research staff, and the biostatistical support team under the direction of Dr. Irina Ostrovnaya. Conference calls will also occur bi-weekly between the DCC and the Study Principal Investigator to discuss the trial.

Case Report Forms with accompanying source documents must be provided to the DCC to ensure that

real-time monitoring can be accomplished. Queries will be generated by the DCC as needed if questions arise, and prompt responses are requested back to the DCC. Internal audits will be conducted by the DCC. Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the DCC for audit, or (2) selected patient records may be audited on-site at participating sites. These audits will be performed by persons who are qualified by training and experience to monitor the progress of the investigation. During these audits the following activities will take place:

- Review regulatory binders for protocol documentation;
- Ensure that case report forms are source data verified according to the monitoring plan;
- Verify drug accountability is complete and accurate; and
- Verify compliance to GCPs, ICH guidelines, FDA regulations, and applicable SOPs.

If there is ever an audit at the DCC, then the DCC is responsible for having all source documents, research records, all IRB approval documents, Drug Accountability Record Forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

16.7 Data and Safety Monitoring

The Data and Safety Monitoring Committee (DSMC) under the direction of Dr. Robert Motzer and Bonnie Edelman, Manager, will be responsible for monitoring the data safety of the open and closed to accrual protocols sponsored by POETIC. The DSMC meets quarterly, and will review data quarterly, semi annually or annually based on the risk level of the protocol. A copy of the MSKCC Data and Safety Monitoring Plans is on file at the Data and Coordinating Center.

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were initially created and approved by the National Cancer Institute in September 2001. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/clinicaltrials/conducting/dsm-guidelines. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://mskweb2.mskcc.org/irb/index.htm. The Data and Safety Monitoring Committee (DSMC) monitors all Phase I and II clinical trials and reports to the Research Council and Institutional Review Board.

16.8 Therapeutic Response Review

The Therapeutic Response Review Committee (TRRC) is MSKCC's independent response review committee which annually evaluates therapeutic responses for participants in IRB/PB approved clinical trials where therapeutic efficacy is a stated primary objective, typically phase II and III trials. The process, done in an unbiased blinded fashion, ensures the data from the institution's therapeutic trials clinical research program is verified and vetted. Studies monitored by the TRRC include NCI-NIH, in-house, industrial trials, and multi-center trials where MSKCC is the coordinating center, which are not reviewed by an outside independent therapeutic response review board.

MSKCC's TRRC review will serve as the committee that may review and confirm responses of

POETIC patients. The TRRC will possibly randomly select cases on an annual basis. If a patient is selected to be reviewed by the TRRC, the clinical site will be notified by the DCC with the required materials to be submitted to the committee and timeframe of submission.

17.1 PROTECTION OF HUMAN SUBJECTS

17.2 Privacy

All institutional, FDA, and NCI requirements for human subjects must be met. This study will be carried out in compliance with the regulations of the Health Insurance Portability and Accountability Act (HIPAA). Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The POETIC DCC is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site. The DCC is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.

The risks and benefits of participation in this study will be reviewed with the patient and/or parent/legal guardian.

Enrollment on this study is on a voluntary basis and every effort will be made to maintain privacy and confidentiality. The patient's records will be confidential. Only authorized individuals or agencies may inspect the records. No identifying information will be used in reports or publications resulting from this study.

17.3 Serious Adverse Event (SAE) Reporting

The Study Principal Investigator is responsible for monitoring the safety of patients who enroll in the study. All adverse events (AEs) and Serious Adverse Events (SAEs) occurring after any administration of the study drug regardless of drug attribution will be followed to the end of the study including 30 days after the last administration of the study drug, as well as any SAEs designated possibly, probably, or definitely related to treatment that occur greater than 30 days.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be used for adverse event and serious adverse event reporting. All participating sites should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/reporting/ctc.html).

The Study Principal Investigator is required to report all adverse events that occur during the clinical study starting with the first dose of study drug throughout 30 days of stopping the investigational agent. Severe adverse events must be reported to the appropriate protocol-defined study sponsors. Serious adverse events must be reported either by telephone or in person to the Study Principal Investigator, DCC, and local IRB within 24 hours of knowledge of their occurrence. A written SAE report including source documentation must be sent to the Study Principal Investigator and DCC within another 3 calendar days, using the Serious Adverse Event case report form. Additionally, the Study Principal Investigator is responsible for submitting follow-up reports for all SAEs regarding the patient's subsequent course until the SAE has resolved or until the patient's condition stabilizes (in the case of persistent impairment), or the patient dies.

A serious adverse event (SAE) is any adverse drug experience that occurs at any dose that results in any of the following outcomes:

- Death.
- Life-threatening adverse drug experience.
- Requires inpatient hospitalization or prolongation of existing hospitalization grade 2 and above.
- For the purpose of this study, hospitalizations for protocol-scheduled procedures, blood product transfusions, or for social reasons (ie, awaiting transport home) will not be considered SAEs.
- Persistent or significant disability/incapacity.
- A congenital anomaly/birth defect.
- Requires medical or surgical intervention to prevent one of the outcomes listed above.

Reporting requirements for adverse events that occur on treatment and within 30 days[1] of the last dose of study drug

	Grade 1	Grade 2		Grade 2		Grade 3		Grade 3		Grades 4 & 5
	Unexpected and Expected with or with-out hospitalization	Unexpected		Expected		Unexpected		Expected		Unexpected and Expected
		with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	
Unrelated Unlikely	Not Required	SAE Report Required	Not Required	SAE Report Required	Not Required	SAE Report Required	Not Required	SAE Report Required	Not Required	SAE Report Required
Possible Probable Definite	Not Required	SAE Report Required	SAE Report Required	SAE Report Required	Not Required	SAE Report Required	SAE Report Required	SAE Report Required	Not Required	SAE Report Required

[1] Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of study treatment require an SAE report as follows:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

Initial notification for all SAEs must include:

- Grade of event
- Date of event
- A brief description of the event
- Attribution to the investigational agent
- Patient Status

Relationship of any adverse event to study drug should use the following criteria:

- Definite - The adverse event *is clearly related* to protocol therapy.
- Probable - The adverse event *is likely related* to protocol therapy.
- Possible - The adverse event *may be related* to protocol therapy.
- Unlikely - The adverse event *is doubtfully related* to protocol therapy.

- Unrelated - The adverse event *is clearly NOT related* to protocol therapy.

SAEs must be reported within 24 hours by phone or e-mail to:

- DCC
- Study Principal Investigator of the protocol (Dr. Tanya Trippett)
- Local IRB

SAE contact information for the POETIC DCC is listed below:

POETIC Data and Coordinating Center
Memorial Sloan-Kettering Cancer Center
405 Lexington Avenue, Rm 3-512
New York, New York 10174
Telephone: 646-888-5714
Fax: 646-888-5726

Contact information for the Primary Investigator is listed below:

Study Principal Investigator
Tanya Trippett, MD
Memorial Sloan-Kettering Cancer Center
1275 York Avenue
New York, NY 10021
Telephone (212) 639-8267
Fax (212) 717-3239
E-mail: Trippet1@mskcc.org

Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-993-1220) will be provided with the copies of all serious adverse experiences, within two working days. Additionally, any pregnancy occurring in association with use of a Merck Product will be reported to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-993-1220.

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators by the investigator. The investigator will cross reference this submission according to local regulations to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally, a copy of these reports will be submitted to Merck & Co., Inc (Attn: Worldwide Product Safety; FAX 215-993-1220) at the time of the submission.

In the event of an AE, appropriate medical and supportive care will be administered. All efforts will be made to minimize the side effects and to support the patient until the toxicity resolves.

17.2.1Agent-Specific Expected Adverse Events List

The list below guides the investigator in determining which AEs require expedited reporting. Those AEs that do not require expedited reporting are reported in routine study data submissions.

Expected adverse events for **Vorinostat** include:

Likely (> 20%)	Less Likely (≤ 20%)	Rare but Serious (< 3%)
• Anemia • Diarrhea • Nausea • Vomiting • Fatigue • Platelet count decrease • Anorexia	• Abdominal Pain • Constipation • Dry mouth • Dyspepsia • Fever • Infection[2] • Constipation • Alanine aminotransferase increased • Alkaline phosphatase increased • Aspartate aminotransferase increased • Blood bilirubin increased • Creatinine increased • Lympocyte count increased • Neutrophil count decreased • Weight loss • White blood cell decreased • Dehydration • Hyperglycemia • Hypoalbuminemia • Hypocalcemia • Hypokalemia • Hyponatremia • Hypophosphatemia • Musculoskeletal and connective tissue disorder- other (muscle spasms) • Muscle weakness[3] • Dizziness • Dysgeusia • Cough • Dyspnea • Alopecia	• Skin and subcutaneous tissue disorders- Other (skin necrosis)

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

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

[3]Muscle weakness includes Generalized muscle weakness, Muscle weakness left-sided, Muscle weakness lower limb, Muscle weakness right-sided, Muscle weakness trunk, and Muscle weakness upper limb under the MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS SOC.

[4]Prolongation of prothrombin time and International Normalized Ratio have been observed in patients using vorinostat concomitantly with coumarin-derivative anticoagulants.

Also reported on vorinostat (SAHA) trials but with the relationship to vorinostat (SAHA) still undetermined:

Blood and lymphatic system disorders - Febrile neutropenia
Cardiac disorders - Atrial fibrillation; Atrial flutter; Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Ventricular fibrillation
Ear and labyrinth disorders - Tinnitus; Vertigo
Eye disorders - Blurred vision
Gastrointestinal disorders - Abdominal distension; Anal hemorrhage; Bloating; Cheilitis; Colitis; Dysphagia; Esophageal hemorrhage; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis; Gingival pain; Lower gastrointestinal hemorrhage; Mucositis oral; Oral hemorrhage; Small intestinal obstruction; Stomach pain; Upper gastrointestinal hemorrhage
General disorders and administration site conditions - Chills; Death NOS; Edema limbs; Gait disturbance; General disorders and administration site conditions - Other (angioedema); General disorders and administration site conditions - Other (failure to thrive); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
Hepatobiliary disorders - Hepatic failure
Infections and infestations - Infections and infestations - Other (Herpes zoster)
Injury, poisoning and procedural complications - Bruising; Vascular access complication; Wound dehiscence
Investigations - Activated partial thromboplastin time prolonged[4]; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased[4]; Investigations - Other (elevated LDH); Lipase increased
Metabolism and nutrition disorders - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hypernatremia; Hypoglycemia; Hypomagnesemia; Tumor lysis syndrome
Musculoskeletal and connective tissue disorders - Arthralgia; Back pain; Chest wall pain; Myalgia; Neck pain; Pain in extremity
Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain
Nervous system disorders - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysphasia; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (Guillain-Barre syndrome); Nervous system disorders - Other (head injury); Nervous system disorders - Other (polyneuropathy); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Syncope; Tremor
Psychiatric disorders - Agitation; Anxiety; Confusion; Depression; Insomnia; Personality change; Psychosis

Renal and urinary disorders - Acute kidney injury; Hematuria; Proteinuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
Reproductive system and breast disorders - Pelvic pain; Uterine hemorrhage
Respiratory, thoracic and mediastinal disorders - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Nasal congestion; Pharyngeal mucositis; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis
Skin and subcutaneous tissue disorders - Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash maculo-papular
Vascular disorders - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event; Vascular disorders - Other (arterial thrombosis); Vasculitis

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

The effects of vorinostat on a fetus and reproductive organs have not been studied and are therefore unknown. It is not known whether vorinostat can cause teratogenic changes to the fetus or the consequences to an unborn child. Patients who are pregnant or nursing, planning to become pregnant or to father a child are not permitted to enroll on this study. Women of childbearing potential must have a negative pregnancy test before the start of treatment on the study.

An adequate form of contraception must be used by both male and female patients and their partners during therapy with vorinostat. It is recommended that two forms of birth control be used simultaneously unless abstinence is the chosen method.

Expected adverse events for **Etoposide** include:

Likely (> 20%)	Less Likely (≤ 20%)	Rare but Serious (< 3%)
• Nausea and vomiting • Hair loss • Feeing of weakness or tiredness • Fewer white blood cells, red blood cells and platelets in the blood. ○ A low number of red blood cells can make you feel tired and weak	• Loss of appetite • Decreased blood pressure during the infusion which may require treatment • Rashes • Diarrhea • Pain in the abdomen • Mouth sores • Tingling sensation or loss of sensation in fingers or toes • A feeling of extreme tiredness or weakness	• Damage to the liver • Severe allergic reaction which can be life threatening with shortness of breath, low blood pressure, rapid heart rate, chills and fever • New cancer or leukemia resulting from this treatment • Severe rashes which can result in loss of skin and damage to mucous membranes

○ A low number of white blood cells can make it easier to get infections ○ A low number of platelets may cause you to bruise and bleed more easily	• Loosening of the fingernails or toenails from their nail beds • Inflammation of the vein through which the medication was given • Chest pain	• Absence or decrease monthly periods which may be temporary or permanent and may make it difficult to have children • Damage to the heart muscle which may make you feel tired, weak, feel short of breath, and retain fluid

17.2.2 SAE Reporting (This section pertains to guidelines for Memorial Sloan-Kettering only)

The DCC RSA must submit any SAEs to the MSKCC IRB/PB as soon as possible but no later than 5 calendar days. The MSKCC IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org**.** The report will be generated by the DCC RSA, and should contain the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following:
  - A explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:

The CRDB AE report should be completed as above and the FDA assigned IND/IDE number written at the top of the report. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

19.0 REFERENCE(S)

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