Phase 1b/2 Study of Vorinostat in Combination with Gemcitabine and Docetaxel in Advanced Sarcoma

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SCHEMA/SYNOPSIS

Phase 1b:

For the Phase 1b portion of the study, dose escalation will follow a "3+3" schema, the dose levels are the following:

Dose Level	Docetaxel IV Day 8	Gemcitabine IV (Days 1 and 8)	Vorinostat Orally (Days -1 to +2 and 7-9)
-2	75 mg/m^2	675 mg/m^2	200 mg daily
-1	75 mg/m^2	900 mg/m^2	200 mg daily
1	75 mg/m^2	900 mg/m^2	300 mg daily
2	75 mg/m^2	900 mg/m^2	200 mg twice a day (total 400 mg)
3	75 mg/m^2	900 mg/m^2	300 mg twice a day (total 600 mg)
4	75 mg/m^2	900 mg/m^2	400 mg twice a day (total 800 mg)

Phase 2:

The recommended Phase 2 dose (RP2D) will be taken to the next portion of the trial which is a single arm, open-label, Phase 2 trial of gemcitabine/docetaxel + vorinostat to be investigated in patients with advanced sarcomas.

Eligible patients will be required to have advanced metastatic or unresectable soft tissue sarcomas that have received up to 2 prior lines of systemic cytotoxic chemotreatment. Patients with Ewing's sarcoma, osteosarcoma, GIST, low grade chondrosarcoma, and chordoma are excluded.

We will employ Simon's Optimal two-stage design with a total of 17 evaluable patients in the first stage. To continue to full accrual based on 6-month Progression-Free Survival Rate (PFR), at least 4 patients out of the first 17 must be progression-free at six months. If the study passes this interim condition, accrual will continue to a total of 37 patients, where progression-free at six months in at least 11 patients is required to deem the agent promising.

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Phase 1b

To determine the dose of vorinostat that can be safely combined with gemcitabine and docetaxel in patients with advanced sarcomas.

1.1.2 Phase 2

To determine the safety and efficacy of gemcitabine and docetaxel in combination with vorinostat in patients with advanced sarcomas. The hypothesis is that gemcitabine and docetaxel + vorinostat will be safe and will improve the 6-months progression-free rates (PFR) of the combination by 20% (from 20% to 40%).

1.2 Secondary Objectives

1.2.1 Phase 2

- To determine the objective response rate, progression-free, and overall survival of patients with advanced sarcomas treated with gemcitabine and docetaxel + vorinostat;

1.3 Exploratory Objective

1.3.1 Phase 1b

To characterize the Pharmacokinetics (PK) and Pharmacodynamics (PD) of vorinostat when combined with gemcitabine and docetaxel in patients with advanced sarcomas.1.3.2 Phase 2

To develop a predictive molecular signature of response to chemotreatment in advanced sarcomas (if enough tumor tissue available).

2. BACKGROUND

2.1 Soft Tissue Sarcomas

Soft tissue and bone sarcomas represent approximately 1-2% of all malignancies in North America, but the morbidity is great in that the peak incidence of many sarcomas is seen in children and young adults (1, 2). Unlike epithelial tumors that increase in frequency with age, sarcomas occur at all ages and a second peak occurs at late middle age, resulting in significant morbidity in productive adults. Although the primary treatment of these tumors has improved, with limb-sparing surgery and radiation treatment resulting in improved functional ability, and adjuvant or neo-adjuvant chemotreatment in bone and select soft tissue sarcomas, the treatment of metastatic disease is unsatisfactory and systemic chemotreatment is of limited value (3, 4, 5). The response rate of metastatic sarcoma to second-line agents is generally less than 15% and the 6-month progression-free survival rate is less than 20% (6). Van Glabekke et al. performed a meta-analysis of 1154 metastatic sarcoma patients that were

treated on 12 clinical trials and generated benchmarks for Phase 2 clinical trial design. In this analysis, the response rate of metastatic sarcoma to second-line agents was generally less than 15% and the 3-month progression-free survival rate (PRF) is less than 20%. They also indicated that an improvement in PFR to more than 40% indicated a regimen with activity in metastatic sarcoma (6). Single agent doxorubicin, single-agent high dose ifosfamide, and combinations including both agents with or without dacarbazine have resulted in modest response rates but no improvement in overall survival. Recently, the combination of gemcitabine and docetaxel achieved no improvement in response rates in the second line setting but some improvement in overall survival in a small randomized Phase 2 trial (7). There is an urgent need to improve the therapies of sarcomas with the development of novel agents or novel combinations that improve outcomes of advanced sarcoma patients.

2.2 Vorinostat

2.2.1 Description

Zolinza® is approved in the US 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. Zolinza® contains vorinostat, which is described chemically as *N*-hydroxy-*N′*-phenyloctanediamide. The empirical formula is $C_{14}H_{20}N_2O_3$. The molecular weight is 264.32. Vorinostat is a white to light orange powder. It is very slightly soluble in water, slightly soluble in ethanol, isopropanol and acetone, freely soluble in dimethyl sulfoxide and insoluble in methylene chloride. It has no chiral centers and is non-hygroscopic. The differential scanning calorimetry ranged from 161.7 (endotherm) to 163.9°C. The pH of saturated water solutions of vorinostat drug substance was 6.6. The pKa of vorinostat was determined to be 9.2. Each 100 mg ZOLINZA 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 sodium lauryl sulfate (8).

2.2.2 Clinical pharmacology

2.2.2.1 Mechanism of Action

Vorinostat inhibits the enzymatic activity of histone deacetylases HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II) at nanomolar concentrations (IC50<86 nM). These enzymes catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. In some cancer 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. *In vitro*, vorinostat causes the accumulation of acetylated histones and induces cell cycle arrest and/or apoptosis of some transformed cells. The mechanism of the antineoplastic effect of vorinostat has not been fully characterized.

2.2.2.2 Pharmacodynamics

Cardiac Electrophysiology: A randomized, partially-blind, placebo-controlled, 2-period crossover study was performed to assess the effects of a single 800-mg dose of vorinostat on the QTc interval in 24 patients with advanced cancer. This study was conducted to assess the impact of vorinostat on ventricular repolarization. The upper bound of the 90% confidence interval of the placebo-adjusted mean QTc interval change-from-baseline was less than 10 msec at every time point through 24 hours. Based on these study results, administration of a single supratherapeutic 800-mg dose of vorinostat does not appear to prolong the QTc interval in patients with advanced cancer; however the study did not include a positive control to demonstrate assay sensitivity. In the fasted state, oral administration of a single 800-mg dose of vorinostat resulted in a mean AUC and C_{max} and median T_{max} of 8.6±5.7 μM●hr and 1.7±0.67 μM and 2.1 (0.5-6) hours, respectively.

In clinical studies in patients with CTCL, three of 86 CTCL patients exposed to 400 mg once daily had Grade 1 (>450-470 msec) or 2 (>470-500 msec or increase of >60 msec above baseline) clinical adverse events of QTc prolongation. In a retrospective analysis of three Phase 1 and two Phase 2 studies, 116 patients had a baseline and at least one follow-up ECG. Four patients had Grade 2 (>470-500 msec or increase of >60 msec above baseline) and 1 patient had Grade 3 (>500 msec) QTc prolongation. In 49 non-CTCL patients from 3 clinical trials who had complete evaluation of QT interval, 2 had QTc measurements of >500 msec and 1 had a QTc prolongation of >60 msec.

2.2.2.3 Pharmacokinetics

2.2.2.3.1 Absorption

The pharmacokinetics of vorinostat were evaluated in 23 patients with relapsed or refractory advanced cancer. After oral administration of a single 400-mg dose of vorinostat with a high-fat meal, the mean ± standard deviation area under the curve (AUC) and peak serum concentration (C_{max}) and the median (range) time to maximum concentration (T_{max}) were 5.5±1.8 μM●hr, 1.2±0.62 μM and 4 (2-10) hours, respectively.

In the fasted state, oral administration of a single 400-mg dose of vorinostat resulted in a mean AUC and C_{max} and median T_{max} of 4.2±1.9 μM●hr and 1.2±0.35 μM and 1.5 (0.5-10) hours, respectively. Therefore, oral administration of vorinostat with a high-fat meal resulted in an increase (33%) in the extent of absorption and a modest decrease in the rate of

absorption (T_{max} delayed 2.5 hours) compared to the fasted state. However, these small effects are not expected to be clinically meaningful. In clinical trials of patients with CTCL, vorinostat was taken with food.

At steady state in the fed-state, oral administration of multiple 400-mg doses of vorinostat resulted in a mean AUC and C_{max} and a median T_{max} of 6.0±2.0 μM●hr, 1.2±0.53 μM and 4 (0.5-14) hours, respectively.

2.2.2.3.2 Distribution

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

2.2.2.3.3 Metabolism

The major pathways of vorinostat metabolism involve glucuronidation and hydrolysis followed by β-oxidation. Human serum levels of two metabolites, *O*-glucuronide of vorinostat and 4-anilino4-oxobutanoic acid were measured. Both metabolites are pharmacologically inactive. Compared to vorinostat, the mean steady state serum exposures in humans of the *O*-glucuronide of vorinostat and 4-anilino-4-oxobutanoic acid were 4-fold and 13-fold higher, respectively.

In vitro studies using human liver microsomes indicate negligible biotransformation by cytochromes P450 (CYP).

2.2.2.3.4 Excretion

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. The mean urinary recovery of two pharmacologically inactive metabolites at steady state was 16±5.8% of vorinostat dose as the *O*-glucuronide of vorinostat, and 36±8.6% of vorinostat dose as 4-anilino-4-oxobutanoic acid. Total urinary recovery of vorinostat and these two metabolites averaged 52±13.3% of vorinostat dose. The mean terminal half-life (t½) was ~2.0 hours for both vorinostat and the *O*-glucuronide metabolite, while that of the 4-anilino-4-oxobutanoic acid metabolite was 11 hours.

2.2.2.3.5 Special Populations

Based upon an exploratory analysis of limited data, gender, race, and age do not appear to have meaningful effects on the pharmacokinetics of vorinostat.

Pediatric: Vorinostat was not evaluated in patients <18 years of age.

Hepatic Insufficiency: Vorinostat was studied in a limited number of patients with hepatic impairment. Based on these limited data, vorinostat is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild and moderate

hepatic impairment.

Renal Insufficiency: Vorinostat was not evaluated in patients with renal impairment. However, renal excretion does not play a role in the elimination of vorinostat.

2.2.2.3.6 Pharmacokinetic effects of vorinostat with other agents

Vorinostat is not an inhibitor of CYP drug metabolizing enzymes in human liver microsomes at steady state C_{max} of the 400 mg dose (C_{max} of 1.2 μM vs IC50 of >75 μM). Gene expression studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 activities by vorinostat at concentrations higher (≥10 μM) than pharmacologically relevant. 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.

In vitro studies indicate that vorinostat is not a substrate of human P-glycoprotein (P-gp). In addition, vorinostat has no inhibitory effect on human P-gp-mediated transport of vinblastine (a marker P-gp substrate) at concentrations of up to 100 μM. Thus, vorinostat is not likely to inhibit P-gp at the pharmacologically relevant serum concentration of 2 μM (C_{max}) in humans.

2.2.3 Nonclinical toxicology - Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been performed with vorinostat.

Vorinostat was mutagenic *in vitro* in the bacterial reverse mutation assays (Ames test), caused chromosomal aberrations *in vitro* in Chinese hamster ovary (CHO) cells and increased the incidence of micro-nucleated erythrocytes when administered to mice (Mouse Micronucleus Assay).

Effects on the female reproductive system were identified in the oral fertility study when females were dosed for 14 days prior to mating through gestational day 7. Doses of 15, 50, and 150 mg/kg/day to rats resulted in approximate exposures of 0.15, 0.36, and 0.70 times the expected clinical exposure based on AUC. Dose dependent increases in corpora lutea were noted at ≥15 mg/kg/day, which resulted in increased peri-implantation losses were noted at ≥50 mg/kg/day. At 150 mg/kg/day, there were increases in the incidences of dead fetuses and in resorptions.

No effects on reproductive performance were observed in male rats dosed (20, 50, 150 mg/kg/day; approximate exposures of 0.15, 0.36, and 0.70 times the expected clinical exposure based on AUC), for 70 days prior to mating with untreated females.

2.3 Gemcitabine

2.3.1 Description

Gemcitabine is a nucleoside metabolic inhibitor that exhibits antitumor activity. Gemcitabine HCl is 2′-deoxy-2′,2′-difluorocytidine monohydrochloride (β-isomer). The empirical

formula for gemcitabine HCl is $C_9H_{11}F_2N_3O_4$ • HCl. It has a molecular weight of 299.66 (9).

Gemcitabine HCl is a white to off-white solid. It is soluble in water, slightly soluble in methanol, and practically insoluble in ethanol and polar organic solvents. The clinical formulation is supplied as a sterile solution for intravenous single vial use only. Vials of gemcitabine injection contain either 200 mg, 1 g, or 2 g of gemcitabine HCl (expressed as free base). Each mL contains equivalent of 38 mg of gemcitabine in water for injection, USP. Hydrochloric acid and/or sodium hydroxide may have been added for pH adjustment.

2.3.2 Clinical pharmacology

2.3.2.1 Mechanism of Action

Gemcitabine exhibits cell phase specificity, primarily killing cells undergoing DNA synthesis (S-phase) and also blocking the progression of cells through the G1/S-phase boundary. Gemcitabine is metabolized intracellularly by nucleoside kinases to the active diphosphate (dFdCDP) and triphosphate (dFdCTP) nucleosides. The cytotoxic effect of gemcitabine is attributed to a combination of two actions of the diphosphate and the triphosphate nucleosides, which leads to inhibition of DNA synthesis. First, gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for catalyzing the reactions that generate the deoxynucleoside triphosphates for DNA synthesis. Inhibition of this enzyme by the diphosphate nucleoside causes a reduction in the concentrations of deoxynucleotides, including dCTP. Second, gemcitabine triphosphate competes with dCTP for incorporation into DNA. The reduction in the intracellular concentration of dCTP (by the action of the diphosphate) enhances the incorporation of gemcitabine triphosphate into DNA (self-potentiation). After the gemcitabine nucleotide is incorporated into DNA, only one additional nucleotide is added to the growing DNA strands. After this addition, there is inhibition of further DNA synthesis. DNA polymerase epsilon is unable to remove the gemcitabine nucleotide and repair the growing DNA strands (masked chain termination). In CEM T lymphoblastoid cells, gemcitabine induces internucleosomal DNA fragmentation, one of the characteristics of programmed cell death.

2.3.2.2 Pharmacodynamics

Gemcitabine demonstrated dose-dependent synergistic activity with cisplatin *in vitro*. No effect of cisplatin on gemcitabine triphosphate accumulation or DNA double-strand breaks was observed. *In vivo*, gemcitabine showed activity in combination with cisplatin against the LX-1 and CALU-6 human lung xenografts, but minimal activity was seen with the NCI-H460 or NCI-H520 xenografts. Gemcitabine was synergistic with cisplatin in the Lewis lung murine xenograft. Sequential exposure to gemcitabine 4 hours before cisplatin produced the greatest interaction.

2.3.2.3 Pharmacokinetics

2.3.2.3.1 Absorption and Distribution

The pharmacokinetics of gemcitabine were examined in 353 patients, with various solid tumors. Pharmacokinetic parameters were derived using data from patients treated for varying durations of treatment given weekly with periodic rest weeks and using both short infusions (<70 minutes) and long infusions (70 to 285 minutes). The total gemcitabine dose varied from 500 to 3600 mg/m^2.

The volume of distribution was increased with infusion length. Volume of distribution of gemcitabine was 50 L/m^2 following infusions lasting <70 minutes. For long infusions, the volume of distribution rose to 370 L/m^2. Gemcitabine pharmacokinetics are linear and are described by a 2-compartment model. Population pharmacokinetic analyses of combined single and multiple dose studies showed that the volume of distribution of gemcitabine was significantly influenced by duration of infusion and gender. Gemcitabine plasma protein binding is negligible.

2.3.2.3.2 Metabolism

Gemcitabine disposition was studied in 5 patients who received a single 1000 mg/m^2/30 minute infusion of radiolabeled drug. Within one (1) week, 92% to 98% of the dose was recovered, almost entirely in the urine. Gemcitabine (<10%) and the inactive uracil metabolite, 2′-deoxy-2′,2′-difluorouridine (dFdU), accounted for 99% of the excreted dose. The metabolite dFdU is also found in plasma. The active metabolite, gemcitabine triphosphate, can be extracted from peripheral blood mononuclear cells. The half-life of the terminal phase for gemcitabine triphosphate from mononuclear cells ranges from 1.7 to 19.4 hours.

2.3.2.3.3 Excretion

Clearance of gemcitabine was affected by age and gender. The lower clearance in women and the elderly results in higher concentrations of gemcitabine for any given dose. Differences in either clearance or volume of distribution based on patient characteristics or the duration of infusion result in changes in half-life and plasma concentrations. Table 1 shows plasma clearance and half-life of gemcitabine following short infusions for typical patients by age and gender.

Table 1. Clearance and Half-life based on patient characteristics

Gemcitabine Clearance and Half-Life for the "Typical" Patient Age	Clearance Men (L/hr/m^2)	Clearance Women (L/hr/m^2)	Half-Life Men (min)	Half-Life Women (min)
29	92.2	69.4	42	49

45	75.7	57.0	48	57
65	55.1	41.5	61	73
79	40.7	30.7	79	94

Gemcitabine half-life for short infusions ranged from 42 to 94 minutes, and the value for long infusions varied from 245 to 638 minutes, depending on age and gender, reflecting a greatly increased volume of distribution with longer infusions.

2.3.2.3.4 Drug Interactions

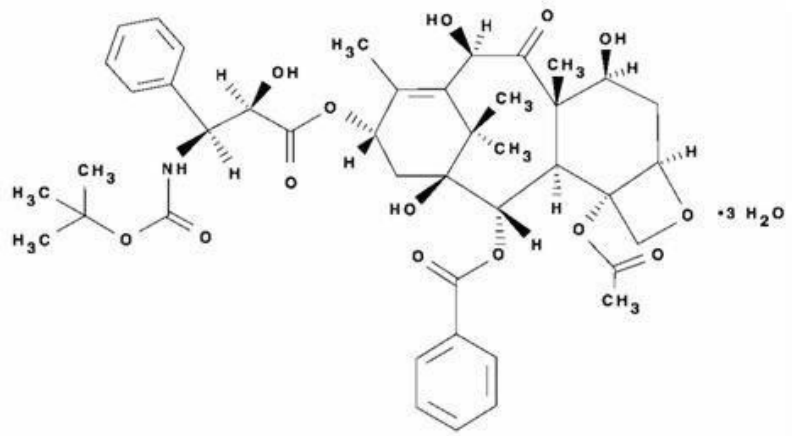
When gemcitabine (1250 mg/m^2 on Days 1 and 8) and cisplatin (75 mg/m^2 on Day 1) were administered in NSCLC patients, the clearance of gemcitabine on Day 1 was 128 L/hr/m^2 and on Day 8 was 107 L/hr/m^2. The clearance of cisplatin in the same study was reported to be 3.94 mL/min/m^2 with a corresponding half-life of 134 hours. Analysis of data from metastatic breast cancer patients shows that, on average, gemcitabine has little or no effect on the pharmacokinetics (clearance and half-life) of paclitaxel and paclitaxel has little or no effect on the pharmacokinetics of gemcitabine. Data from NSCLC patients demonstrate that gemcitabine and carboplatin given in combination does not alter the pharmacokinetics of gemcitabine or carboplatin compared to administration of either single-agent. However, due to wide confidence intervals and small sample size, interpatient variability may be observed.

2.3.3 Nonclinical toxicology - *Carcinogenesis, Mutagenesis, Impairment of Fertility*

Long-term animal studies to evaluate the carcinogenic potential of gemcitabine have not been conducted. Gemcitabine induced forward mutations in vitro in a mouse lymphoma (L5178Y) assay and was clastogenic in an in vivo mouse micronucleus assay. Gemcitabine was negative when tested using the Ames, in vivo sister chromatid exchange, and in vitro chromosomal aberration assays, and did not cause unscheduled DNA synthesis in vitro. Gemcitabine intraperitoneal doses of 0.5 mg/kg/day (about 1/700 the human dose on a mg/m^2 basis) in male mice had an effect on fertility with moderate to severe hypospermatogenesis, decreased fertility, and decreased implantations. In female mice, fertility was not affected but maternal toxicities were observed at 1.5 mg/kg/day administered intravenously (about 1/200 the human dose on a mg/m^2 basis) and fetotoxicity or embryolethality was observed at 0.25 mg/kg/day administered intravenously (about 1/1300 the human dose on a mg/m^2 basis).

2.4 Docetaxel

Docetaxel is an antineoplastic agent belonging to the taxoid family. It is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. The chemical name for docetaxel is (2R,3S)-N-carboxy-3-phenylisoserine,N-tert-butyl ester, 13-ester with 5β-20-epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4-acetate 2-benzoate, trihydrate. Docetaxel has the following structural formula:



Docetaxel is a white to almost-white powder with an empirical formula of $C_{43}H_{53}NO_{14}$• $3H_2O$, and a molecular weight of 861.9. It is highly lipophilic and practically insoluble in water.

TAXOTERE (docetaxel) injection concentrate is a clear yellow to brownish-yellow viscous solution. TAXOTERE is sterile, non-pyrogenic, and is available in single-dose vials containing 20 mg (0.5 mL) or 80 mg (2 mL) docetaxel (anhydrous). Each mL contains 40 mg docetaxel (anhydrous) and 1040 mg polysorbate 80.

TAXOTERE injection concentrate requires dilution with diluent prior to addition to the infusion bag. A sterile, non-pyrogenic, single-dose diluent is supplied for that purpose. The diluent for TAXOTERE contains 13% ethanol in water for injection, and is supplied in vials (10).

2.4.1 Clinical pharmacology

2.4.1.1 Mechanism of Action

Docetaxel is an antineoplastic agent that acts by disrupting the microtubular network in cells that is essential for mitotic and interphase cellular functions. Docetaxel binds to free tubulin and promotes the assembly of tubulin into stable microtubules while simultaneously inhibiting their disassembly. This leads to the production of microtubule bundles without normal function and to the stabilization of microtubules, which results in the inhibition of mitosis in cells. Docetaxel's binding to microtubules does not alter the number of protofilaments in the bound microtubules, a feature which differs from most spindle poisons currently in clinical use.

2.4.1.2 Human Pharmacokinetics

Absorption: The pharmacokinetics of docetaxel have been evaluated in cancer patients after administration of 20 mg/m^2 to 115 mg/m^2 in Phase 1 studies. The area under the curve (AUC) was dose proportional following doses of 70 mg/m^2 to 115 mg/m^2 with infusion times of 1 to 2 hours. Docetaxel's pharmacokinetic profile is consistent with a three-compartment

pharmacokinetic model, with half-lives for the α, β, and γ phases of 4 min, 36 min, and 11.1 hr, respectively. Mean total body clearance was 21 L/h/m^2.

Distribution: The initial rapid decline represents distribution to the peripheral compartments and the late (terminal) phase is due, in part, to a relatively slow efflux of docetaxel from the peripheral compartment. Mean steady state volume of distribution was 113 L. In vitro studies showed that docetaxel is about 94% protein bound, mainly to α1-acid glycoprotein, albumin, and lipoproteins. In three cancer patients, the in vitro binding to plasma proteins was found to be approximately 97%. Dexamethasone does not affect the protein binding of docetaxel.

Metabolism: In vitro drug interaction studies revealed that docetaxel is metabolized by the CYP3A4 isoenzyme, and its metabolism may be modified by the concomitant administration of compounds that induce, inhibit, or are metabolized by cytochrome P450 3A4.

Elimination: A study of 14C-docetaxel was conducted in three cancer patients. Docetaxel was eliminated in both the urine and feces following oxidative metabolism of the tert-butyl ester group, but fecal excretion was the main elimination route. Within 7 days, urinary and fecal excretion accounted for approximately 6% and 75% of the administered radioactivity, respectively. About 80% of the radioactivity recovered in feces is excreted during the first 48 hours as 1 major and 3 minor metabolites with very small amounts (less than 8%) of unchanged drug.

Effect of Age: A population pharmacokinetic analysis was carried out after TAXOTERE treatment of 535 patients dosed at 100 mg/m^2. Pharmacokinetic parameters estimated by this analysis were very close to those estimated from Phase 1 studies. The pharmacokinetics of docetaxel were not influenced by age.

Effect of Gender: The population pharmacokinetics analysis described above also indicated that gender did not influence the pharmacokinetics of docetaxel.

Hepatic Impairment: The population pharmacokinetic analysis described above indicated that in patients with clinical chemistry data suggestive of mild to moderate liver impairment (AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN), total body clearance was lowered by an average of 27%, resulting in a 38% increase in systemic exposure (AUC). This average, however, includes a substantial range and there is, at present, no measurement that would allow recommendation for dose adjustment in such patients. Patients with combined abnormalities of transaminase and alkaline phosphatase should not be treated with TAXOTERE. Patients with severe hepatic impairment have not been studied.

Effect of Race: Mean total body clearance for Japanese patients dosed at the range of 10 mg/m^2 to 90 mg/m^2 was similar to that of European/American populations dosed at 100

mg/m^2, suggesting no significant difference in the elimination of docetaxel in the two populations.

Effect of Ketoconazole: The effect of ketoconazole (a strong CYP3A4 inhibitor) on the pharmacokinetics of docetaxel was investigated in 7 cancer patients. Patients were randomized to receive either docetaxel (100 mg/m^2 intravenous) alone or docetaxel (10 mg/m^2 intravenous) in combination with ketoconazole (200 mg orally once daily for 3 days) in a crossover design with a 3-week washout period. The results of this study indicated that the mean dose-normalized AUC of docetaxel was increased 2.2-fold and its clearance was reduced by 49% when docetaxel was co-administration with ketoconazole.

Effect of Combination Therapies:

- Dexamethasone: Docetaxel total body clearance was not modified by pretreatment with dexamethasone.
- Cisplatin: Clearance of docetaxel in combination treatment with cisplatin was similar to that previously observed following monotreatment with docetaxel. The pharmacokinetic profile of cisplatin in combination treatment with docetaxel was similar to that observed with cisplatin alone.
- Cisplatin and Fluorouracil: The combined administration of docetaxel, cisplatin, and fluorouracil in 12 patients with solid tumors had no influence on the pharmacokinetics of each individual drug.
- Prednisone: A population pharmacokinetic analysis of plasma data from 40 patients with hormone-refractory metastatic prostate cancer indicated that docetaxel systemic clearance in combination with prednisone is similar to that observed following administration of docetaxel alone.
- Cyclophosphamide and Doxorubicin: A study was conducted in 30 patients with advanced breast cancer to determine the potential for drug-drug-interactions between docetaxel (75 mg/m^2), doxorubicin (50 mg/m^2), and cyclophosphamide (500 mg/m^2) when administered in combination. The coadministration of docetaxel had no effect on the pharmacokinetics of doxorubicin and cyclophosphamide when the three drugs were given in combination compared to coadministration of doxorubicin and cyclophosphamide only. In addition, doxorubicin and cyclophosphamide had no effect on docetaxel plasma clearance when the three drugs were given in combination compared to historical data for docetaxel monotreatment.

2.4.2 Nonclinical toxicology

2.4.2.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies with docetaxel have not been performed. Docetaxel was clastogenic in the in vitro chromosome aberration test in CHO-K1 cells and in the in vivo micronucleus test in mice administered doses of 0.39 to 1.56 mg/kg (about 1/60th to 1/15th the

recommended human dose on a mg/m^2 basis). Docetaxel was not mutagenic in the Ames test or the CHO/HGPRT gene mutation assays.

Docetaxel did not reduce fertility in rats when administered in multiple intravenous doses of up to 0.3 mg/kg (about 1/50th the recommended human dose on a mg/m^2 basis), but decreased testicular weights were reported. This correlates with findings of a 10-cycle toxicity study (dosing once every 21 days for 6 months) in rats and dogs in which testicular atrophy or degeneration was observed at intravenous doses of 5 mg/kg in rats and 0.375 mg/kg in dogs (about 1/3rd and 1/15th the recommended human dose on a mg/m^2 basis, respectively). An increased frequency of dosing in rats produced similar effects at lower dose levels.

2.5 Rationale for the combination

The combination of gemcitabine (Gem) and docetaxel (Tax) has shown significant activity in advanced sarcomas and has been the subject of 3 clinical trials lead by the Sarcoma Alliance for Research through Collaboration (SARC) (SARC002, SARC003, and SARC005) (7,11). In particular, SARC002 established Gem/Tax as an active regimen in sarcomas with modest response rate (16%) but most importantly with significant improvements in progression-free survival (6.2 months as compared to 3 months for Gem alone) and overall survival (17.9 months as compared to 11.5 months for Gem alone) (7). Chemotreatment resistance in solid tumors has been linked to the epigenetic silencing of genes relevant to apoptosis (e.g., DAPK, TMS1 and IGFBP3) and DNA repair (e.g., hMLH1, BRCA1, WRN) (12). The epigenetic modulation of genes takes place through both promoter hypermethylation and modification of the histone core (13). Histone deacetylation by histone deacetylases (HDAC) promotes the formation of a condensed and transcriptionally inactive heterochromatin structure, which leads to aberrant gene silencing and chemotreatment resistance (14). Treatment with HDAC inhibitors (such as vorinostat) leads to increased histone acetylation and results in a more open chromatin structure, which affects gene expression and promotes pro-apoptotic conditions leading to potentiation of cytotoxic chemotreatment. The addition of vorinostat has been reported to significantly enhance the cytotoxicity of gemcitabine in preclinical models of lung and pancreatic cancers (15,16). Vorinostat also enhances the activity of taxanes in preclinical models and in early phase clinical trials (work done in the Phase 1 program of the University of Pittsburgh) (17-19). Prolonged schedules of administration (2 weeks continuously) have been associated with toxicity that prohibited multiple cycles of treatment (19). A Phase 1 study of vorinostat in combination with docetaxel used 14 days of vorinostat administration considered the combination to be too toxic, however it should be noted that growth factor support was not allowed and it is not clear whether the observed incidence of neutropenia was truly higher than docetaxel alone

(20). Higher doses with shorter administration schedules may be more relevant for chemopotentiation and combination with chemotreatment. In addition, we plan to use growth factor support as is standard with the combination of Gem/Tax. We also chose the starting dose of docetaxel to be 75°mg/m^2 given that the dose of 100 mg/m^2 used in the Phase 2 study resulted in a substantial proportion of patients experienced dose-limiting peripheral edema. Most sarcoma oncologists use the lower dose in clinical practice, which makes it even more relevant for a combination study (Maki, the Oncologist, The Oncologist August 2007 vol. 12 no. 8 999). Also, the dose being used for GOG trial of gemcitabine/docetaxel + bevacizumab is 35 mg/m^2 on day 1 and day 8 of docetaxel.

Taken together, those data support a strong rationale for the addition of vorinostat to Gem/Tax to improve the efficacy of the combination. We propose a Phase 1b trial to determine the safe dose of vorinostat to combine with Gem/Tax in a novel dose and schedule, followed by an open-label Phase 2 trial to determine the efficacy of the combination.

2.6 Correlative Studies Background

We will perform pharmacokinetic sampling to evaluate the pharmacokinetics of vorinostat when combined with Gem/Tax. This will be compared to pharmacokinetics of vorinostat after vorinostat alone. Optional tumor biopsies will be performed before and after the first cycle in consenting patients to assess the pharmacodynamic effects of the combination.

3. PATIENT SELECTION

3.1 Eligibility Criteria

- Patients must have histologically confirmed soft tissue sarcoma with evidence of metastatic or unresectable disease.
- Patients must have measurable disease by RECIST 1.1. At least one measurable lesion needs to be outside the field of prior therapeutic radiation or has progressed after radiation,
- Up to 3 prior cytotoxic chemotherapy regimens in the metastatic setting are allowed. Adjuvant chemotherapy or targeted therapy will not be considered a prior line of treatment.
- Age ≥18 years. Because no dosing or adverse event data are currently available on the use of vorinostat in combination with gemcitabine and docetaxel in patients <18 years of age, children are excluded from this study.
- ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A).
- Life expectancy of greater than 12 weeks.
- Patients must have normal organ and marrow function as defined below:
    - leukocytes ≥3,000/μL
    - absolute neutrophil count ≥1,500/μL
    - platelets ≥100,000/μL

- total bilirubin — within normal institutional limits
- AST(SGOT)/ALT(SGPT) — ≤1.5 X institutional upper limit of normal (ULN)
- creatinine — ≤1.5 X institutional upper limit of normal (ULN)

- Peripheral neuropathy, if present, should be ≤ grade 1.
- The effects of vorinostat on the developing human fetus are unknown. For this reason and because the other chemotherapeutic agents used in this trial are known to be teratogenic, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation, and 4 months after completion of study drug administration. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. If pregnancy is confirmed, the patient will be deemed not eligible or if started will be immediately removed from study. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of study participation, and 4 months after completion of study drug administration.
- Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

- The following specific histologic subtypes of soft tissue sarcomas will be excluded: GIST, Kaposi's sarcoma, mesothelioma, dermatofibrosarcoma, chordoma, alveolar soft-part sarcoma. Also, all bone sarcomas are excluded including Ewing's sarcoma, osteosarcoma, GIST, low grade chondrosarcoma, and chordoma.
- Patients who have had treatment with chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to starting study treatment or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.
- Patients who are receiving any other investigational agents.
- Patients with known brain metastases should be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
- History of allergic reactions attributed to compounds of similar chemical or biologic composition to gemcitabine, docetaxel, vorinostat, or G-CSF.
- Patients who have received and progressed on the combination of gemcitabine and docetaxel in the metastatic setting are excluded.
- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
- Pregnant and breastfeeding women are excluded from this study.
- Patients taking concomitant HDAC inhibitors. Use of HDAC inhibitor like compounds such as valproic acid for epilepsy is permitted if there is at least a 2 week wash out.
- HIV-positive patients on combination antiretroviral treatment are ineligible because of

the potential for pharmacokinetic interactions with vorinostat, gemcitabine, and docetaxel. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive treatment. Appropriate studies will be undertaken in patients receiving combination antiretroviral treatment when indicated.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. STUDY TREATMENT PLAN

There is a window of ± 1 week available for rescheduling treatment and/or procedures at the discretion of the Sub-investigator, and as discussed with the Investigator if a course of treatment is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject [i.e. non-UPMC insurance coverage] or reduce travel inconvenience, illness, transportation issues, holidays, family emergencies, etc.).

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 6. Appropriate dose modifications are described in Section 5. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Table 2. Study treatment dose levels

Dose Level	Docetaxel IV Day 8	Gemcitabine IV (Days 1 and 8)	Vorinostat PO (Days -1 to +2 and 7-9)
-2	75 mg/m^2	675 mg/m^2	200 mg once daily
-1	75 mg/m^2	900 mg/m^2	200 mg once daily
1	75 mg/m^2	900 mg/m^2	300 mg once daily
2	75 mg/m^2	900 mg/m^2	200 mg twice daily (total 400 mg)
3	75 mg/m^2	900 mg/m^2	300 mg twice daily (total 600 mg)
4	75 mg/m^2	900 mg/m^2	400 mg twice daily (total 800 mg)

The patient will be requested to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at the end of each course.

4.1 Docetaxel administration

Docetaxel will be given at 75 mg/m^2 IV over 60 minutes on day 8 every 21 days (1 cycle).

4.2 Gemcitabine administration

Gem will be given on days 1 and 8 at 900 mg/m^2 IV over 90 minutes (fixed dose infusion rate at 10 mg/m^2/min) every 21 days (1 cycle). For dose level -2, Gem will be given over 67.5 minutes at 10 mg/m^2/min.

4.3 Vorinostat administration

Vorinostat will be given orally at the specified dose levels (Table 2) on days -1 to +2 and days +7-9 every 21 days (treatment for 3 days starting one day prior to chemotherapy on every cycle).

4.4 Pegfilgrastim administration

All patients will receive Pegfilgrastim on day 9 subcutaneously at 6 mg.

Definition of Dose-Limiting Toxicity

Dose-limiting toxicity (DLT) is defined as the following study drug-related events experienced during Cycle 1:

- Grade 4 neutropenia or thrombocytopenia which lasts at least 7 days.
- Grade 3 or 4 febrile neutropenia.
- Grade 3 or greater non-hematological toxicities; this includes grade 3 or greater diarrhea, nausea or vomiting despite adequate treatment (with loperamide for diarrhea, 5HT3 antagonists, steroids and dopamine antagonist for N/V).
- Inability to deliver the entire treatment regimen within the first cycle secondary to drug-related adverse events.

Management and dose modifications associated with the above adverse events are outlined in Section 5. Dosing will be resumed when hematologic toxicities have recovered to grade 1 or less.

Dose escalation will proceed within each cohort according to the following scheme. Dose-limiting toxicity (DLT) is defined above.

Table 3. Dose Escalation

Number of Patients with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	Enter 3 patients at the next dose level.
≥2	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 out of 3	Enter up to 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. Three (3) additional patients will be entered at the next lowest dose level if only 3 patients were treated previously at that dose.
≤ 2 out of 6 at highest dose level below the maximally administered dose	This is the recommended Phase 2 dose. At least 6 patients will be entered at the recommended phase 2 dose.

4.5 General Concomitant Medication and Supportive Care Guidelines

Because there is a potential for interaction of docetaxel with other concomitantly administered drugs through the cytochrome P450 system, the case report form must capture the concurrent use of all other drugs, over-the-counter medications, or alternative therapies. The Investigator/sub-investigator should be alerted if the patient is taking any agent known to affect or with the potential to affect selected CYP450 isoenzymes.

4.6 Duration of study treatment

In the absence of treatment delays due to adverse event(s), treatment may continue 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, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator (i.e., pregnancy).

4.7 Duration of Follow Up

Patients will be followed for 6 months (± 1 month) after removal from study treatment or until death, whichever occurs first. Patients removed from study treatment for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

4.8 Study calendar

Baseline evaluations are to be conducted within 1 week prior to start of protocol treatment. Scans and x-rays must be done ≤4 weeks prior to the start of treatment. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of treatment.

Cycle/Week	Pre-Study	1/1	1/2	1/3	2/1	2/2	2/3	3/1	3/2	3/3+	Off study treatment
Informed consent	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	← X								→	
Physical exam	X	X						X			X

Vital signs	X	X						X			X
Height	X										
Weight	X	X	X					X	X		X
Performance status	X	X						X			X
CBC w/diff, plts	X	X	X	X			X	X	X	X	X
Serum chemistry[a]	X	X	X	X			X	X	X	X	X
EKG (as indicated)	X										
AE evaluation		← X								→	X
Tumor measurements	X	Tumor measurements are repeated every 6 weeks. Documentation (radiologic) must be provided for patients removed from study for progressive disease.									X
Radiologic evaluation	X	Radiologic measurements should be performed every 6 weeks.									X
B-HCG	X[b]										
Vorinostat		A	A					A	A		
Gemcitabine		B	B					B	B		
Docetaxel			C						C		
G-CSF			D						D		
PK blood samples[c]		X	X								
PD blood samples[d]		X	X								
Tumor biopsies (optional)[e]	X		X								X[e]

A: Vorinostat will be given orally twice a day on days -1 to +2 and 7-9 and ; Dose will be at the assigned dose level, it may be given once daily at some dose levels.
B: Gemcitbaine will be given IV at 900 mg/m^2 (10 mg/m^2/min fixed infusion rate) on days 1 and 8
C: Docetaxel will be given IV at 75 mg/m^2 on day 8 after the completion of gemcitabine
D: G-CSF will be given preferably as pegfilgrastim on day 9 (week 2) at 6 mg subcutaneously
a: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, magnesium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.
b: Serum pregnancy test (women of childbearing potential).
c: See Section 8.1 for sampling times.
d: Whole blood will be collected on day 1 (pre- and post- drug administration) and 8 (pre- and post- drug administration) of

the first 2 cycles only.

e: Fine needle aspirates (FNA) and/or core biopsies of tumor samples will be obtained from consenting patients with accessible, evaluable disease, pre-treatment and on day 8 (after the 3 drugs are administered) of the first cycle and when patients go off study treatment.

Note: There is a window of ± 1 week available for rescheduling treatment and/or procedures at the discretion of the Sub-investigator, and as discussed with the Investigator if a course of treatment is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject's inability to comply with the study calendar (i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject [i.e. non-UPMC insurance coverage] or reduce travel inconvenience, illness, transportation issues, holidays, family emergencies, etc.).

5. DOSING DELAYS/DOSE MODIFICATIONS

Dose modifications for vorinostat during Cycle 1 are not permitted. For subsequent cycles, in the event of dose-limiting toxicities attributable to vorinostat, the dose will be reduced to the lower dose level as indicated in Table 2. For patients receiving 200 mg daily, vorinostat will be discontinued. Vorinostat will be held until toxicity resolves to grade 1 or less.

The following are the guidelines for dose modifications of gemcitabine and docetaxel for the expected adverse events:

Table 4. Dose modification for gemcitabine

Dose Level	Gemcitabine Dose
0	900 mg/m^2
-1	675 mg/m^2
-2	500 mg/m^2

Table 5. Dose modification for docetaxel

Dose Level	Docetaxel Dose
0	75 mg/m^2
-1	55 mg/m^2
-2	40 mg/m^2

Table 6. Dose modification for nausea

Event Name	Nausea	
Grade of Event	**Management/Next Dose for Gemcitabine**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol treatment	Off protocol treatment
*Patients requiring a delay of >2 weeks should go off protocol treatment. **Patients requiring > two dose reductions should go off protocol treatment.		
Recommended management: antiemetics.		

Table 7. Dose modification for vomiting

Event Name	Vomiting	
Grade of Event	**Management/Next Dose for Gemcitabine**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
Grade 4	Off protocol treatment	Off protocol treatment
*Patients requiring a delay of >2 weeks should go off protocol treatment. **Patients requiring > two dose reductions should go off protocol treatment.		
Recommended management: antiemetics.		

Table 8. Dose modification for diarrhea

Event Name	Diarrhea	
Grade of Event	**Management/Next Dose for Gemcitabine**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold* until < Grade 2.	Hold* until < Grade 2.

	Resume at one dose level lower, if indicated.**	Resume at one dose level lower, if indicated.**
Grade 4	Off protocol treatment	Off protocol treatment
*Patients requiring a delay of >2 weeks should go off protocol treatment. **Patients requiring > two dose reductions should go off protocol treatment.		
Recommended management: Loperamide antidiarrheal treatment Dosage schedule: 4 mg at first onset, followed by 2 mg with each loose motion until diarrhea-free for 12 hours (maximum dosage: 16 mg/24 hours) Adjunct anti-diarrheal treatment is permitted and should be recorded when used.		

Table 9. Dose modification for neutropenia

Event Name	Neutropenia	
Grade of Event	**Management/Next Dose for Gemcitabine**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3/4	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should go off protocol treatment. **Patients requiring > two dose reductions should go off protocol treatment.		

Table 10. Dose modification for thrombocytopenia

Event Name	Thrombocytopenia	
Grade of Event	**Management/Next Dose for Gemcitabine**	**Management/Next Dose for Docetaxel**
≤ Grade 1	No change in dose	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3/4	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**	Hold* until < Grade 2. Resume at one dose level lower, if indicated.**
*Patients requiring a delay of >2 weeks should go off protocol treatment. **Patients requiring > two dose reductions should go off protocol treatment.		

6. COMPREHENSIVE ADVERSE EVENTS AND POTENTIAL RISKS LISTS

6.1 Adverse Events List for Vorinostat (From US label)

The most common drug-related adverse reactions can be classified into 4 symptom complexes: gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decrease, vomiting, constipation), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia), and taste disorders (dysgeusia, dry mouth). The most common serious drug-related adverse reactions were pulmonary embolism and anemia.

6.1.1 Clinical Trials Experience

The safety of vorinostat was evaluated in 107 CTCL patients in two single arm clinical

studies in which 86 patients received 400 mg once daily.

The data described below reflect exposure to vorinostat, 400 mg once daily, in the 86 patients for a median number of 97.5 days on treatment (range 2 to 480+ days). Seventeen (19.8%) patients were exposed beyond 24 weeks and 8 (9.3%) patients were exposed beyond 1 year. The population of CTCL patients studied was 37 to 83 years of age, 47.7% female, 52.3% male, and 81.4% white, 16.3% black, and 1.2% Asian or multi-racial.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

6.1.2 Common Adverse Reactions

Table 11 summarizes the frequency of CTCL patients (N=86) treated with 400 mg of oral vorinostat with specific adverse events, regardless of causality, using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI CTCAE, version 4.0).

Table 11. AE frequency of CTCL patients with 400 mg of oral vorinostat

	All Grades		Grades 3-5*	
Adverse Events	n	%	n	%
Fatigue	45	52.3	3	3.5
Diarrhea	45	52.3	0	0.0
Nausea	35	40.7	3	3.5
Dysgeusia	24	27.9	0	0.0
Thrombocytopenia	22	25.6	5	5.8
Anorexia	21	24.4	2	2.3
Weight Decreased	18	20.9	1	1.2
Muscle Spasms	17	19.8	2	2.3
Alopecia	16	18.6	0	0.0
Dry Mouth	14	16.3	0	0.0
Blood Creatinine Increased	14	16.3	0	0.0
Chills	14	16.3	1	1.2
Vomiting	13	15.1	1	1.2
Constipation	13	15.1	0	0.0
Dizziness	13	15.1	1	1.2
Anemia	12	14.0	2	2.3
Decreased Appetite	12	14.0	1	1.2
Peripheral Edema	11	12.8	0	0.0
Headache	10	11.6	0	0.0
Pruritus	10	11.6	1	1.2
Cough	9	10.5	0	0.0
Upper Respiratory Infection	9	10.5	0	0.0
Pyrexia	9	10.5	1	1.2

The frequencies of more severe thrombocytopenia, anemia, and fatigue were increased at doses higher than 400 mg once daily of vorinostat.

6.1.3 Serious Adverse Reactions

The most common serious adverse events, regardless of causality, in the 86 CTCL patients in two clinical studies were pulmonary embolism reported in 4.7% (4/86) of patients, squamous cell carcinoma reported in 3.5% (3/86) of patients, and anemia reported in 2.3% (2/86) of patients. There were single events of cholecystitis, death (of unknown cause), deep vein thrombosis, enterococcal infection, exfoliative dermatitis, gastrointestinal hemorrhage, infection, lobar pneumonia, myocardial infarction, ischemic stroke, pelvi-ureteric obstruction, sepsis, spinal cord injury, streptococcal bacteremia, syncope, T-cell lymphoma, thrombocytopenia, and ureteric obstruction.

6.1.4 Discontinuations

Of the CTCL patients who received the 400-mg once daily dose, 9.3% (8/86) of patients discontinued vorinostat due to adverse events. These adverse events, regardless of causality, included anemia, angioneurotic edema, asthenia, chest pain, exfoliative dermatitis, death, deep vein thrombosis, ischemic stroke, lethargy, pulmonary embolism, and spinal cord injury.

6.1.5 Dose Modifications

Of the CTCL patients who received the 400-mg once daily dose, 10.5% (9/86) of patients required a dose modification of vorinostat due to adverse events. These adverse events included increased serum creatinine, decreased appetite, hypokalemia, leukopenia, nausea, neutropenia, thrombocytopenia, and vomiting. The median time to the first adverse event resulting in dose reduction was 42 days (range 17 to 263 days).

6.1.6 Laboratory Abnormalities

Laboratory abnormalities were reported in all of the 86 CTCL patients who received the 400-mg once-daily dose.

Increased serum glucose was reported as a laboratory abnormality in 69% (59/86) of CTCL patients who received the 400-mg once daily dose; only 4 of these abnormalities were severe (Grade 3). Increased serum glucose was reported as an adverse event in 8.1% (7/86) of CTCL patients who received the 400-mg once daily dose.

Transient increases in serum creatinine were detected in 46.5% (40/86) of CTCL patients who received the 400-mg once daily dose. Of these laboratory abnormalities, 34 were NCI CTCAE Grade 1, 5 were Grade 2, and 1 was Grade 3.

Proteinuria was detected as a laboratory abnormality (51.4%) in 38 of 74 patients tested. The

clinical significance of this finding is unknown.

6.1.7 Dehydration

Based on reports of dehydration as a serious drug-related adverse event in clinical trials, patients were instructed to drink at least 2 liters/day of fluids for adequate hydration.

6.1.8 Adverse Reactions in Non-CTCL Patients

The frequencies of individual adverse events were substantially higher in the non-CTCL population. Drug-related serious adverse events reported in the non-CTCL population which were not observed in the CTCL population included single events of blurred vision, asthenia, hyponatremia, tumor hemorrhage, Guillain-Barré syndrome, renal failure, urinary retention, cough, hemoptysis, hypertension, and vasculitis.

6.2 Adverse Event List for Gemcitabine

6.2.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Most adverse reactions are reversible and do not need to result in discontinuation, although doses may need to be withheld or reduced.

Gemzar has been used in a wide variety of malignancies, both as a single-agent and in combination with other cytotoxic drugs.

Single-Agent Use

Myelosuppression is the principal dose-limiting toxicity with Gemzar treatment. Dosage adjustments for hematologic toxicity are frequently needed.

Hematologic — In studies in pancreatic cancer myelosuppression is the dose-limiting toxicity with Gemzar, but <1% of patients discontinued treatment for either anemia, leukopenia, or thrombocytopenia. Red blood cell transfusions were required by 19% of patients. The incidence of sepsis was less than 1%. Petechiae or mild blood loss (hemorrhage), from any cause, was reported in 16% of patients; less than 1% of patients required platelet transfusions. Patients should be monitored for myelosuppression during Gemzar treatment and dosage modified or suspended according to the degree of hematologic toxicity.

Gastrointestinal — Nausea and vomiting were commonly reported (69%) but were usually of mild to moderate severity. Severe nausea and vomiting (WHO Grade 3/4) occurred in <15% of patients. Diarrhea was reported by 19% of patients, and stomatitis by 11% of patients.

Hepatic — In clinical trials, Gemzar was associated with transient elevations of one or both

serum transaminases in approximately 70% of patients, but there was no evidence of increasing hepatic toxicity with either longer duration of exposure to Gemzar or with greater total cumulative dose. Serious hepatotoxicity, including liver failure and death, has been reported very rarely in patients receiving Gemzar alone or in combination with other potentially hepatotoxic drugs.

Renal — In clinical trials, mild proteinuria and hematuria were commonly reported. Clinical findings consistent with the Hemolytic Uremic Syndrome (HUS) were reported in 6 of 2429 patients (0.25%) receiving Gemzar in clinical trials. Four patients developed HUS on Gemzar treatment, 2 immediately post treatment. The diagnosis of HUS should be considered if the patient develops anemia with evidence of microangiopathic hemolysis, elevation of bilirubin or LDH, reticulocytosis, severe thrombocytopenia, and/or evidence of renal failure (elevation of serum creatinine or BUN). Gemzar treatment should be discontinued immediately. Renal failure may not be reversible even with discontinuation of treatment and dialysis may be required.

Fever — The overall incidence of fever was 41%. This is in contrast to the incidence of infection (16%) and indicates that Gemzar may cause fever in the absence of clinical infection. Fever was frequently associated with other flu-like symptoms and was usually mild and clinically manageable.

Rash — Rash was reported in 30% of patients. The rash was typically a macular or finely granular maculopapular pruritic eruption of mild to moderate severity involving the trunk and extremities. Pruritus was reported for 13% of patients.

Pulmonary — In clinical trials, dyspnea, unrelated to underlying disease, has been reported in association with Gemzar treatment. Dyspnea was occasionally accompanied by bronchospasm. Pulmonary toxicity has been reported with the use of Gemzar *[see Adverse Reactions (6.2)]*. The etiology of these effects is unknown. If such effects develop, Gemzar should be discontinued. Early use of supportive care measures may help ameliorate these conditions.

Edema — Edema (13%), peripheral edema (20%), and generalized edema (<1%) were reported. Less than 1% of patients discontinued due to edema.

Flu-like Symptoms — Flu syndrome was reported for 19% of patients. Individual symptoms of fever, asthenia, anorexia, headache, cough, chills, and myalgia were commonly reported. Fever and asthenia were also reported frequently as isolated symptoms. Insomnia, rhinitis, sweating, and malaise were reported infrequently. Less than 1% of patients discontinued due to flu-like symptoms.

Infection — Infections were reported for 16% of patients. Sepsis was rarely reported (<1%).

Alopecia — Hair loss, usually minimal, was reported by 15% of patients.

Neurotoxicity — There was a 10% incidence of mild paresthesias and a <1% rate of severe paresthesias.

Extravasation — Injection-site related events were reported for 4% of patients. There were no reports of injection site necrosis. Gemzar is not a vesicant.

Allergic — Bronchospasm was reported for less than 2% of patients. Anaphylactoid reaction has been reported rarely. Gemzar should not be administered to patients with a known hypersensitivity to this drug.

Cardiovascular — During clinical trials, 2% of patients discontinued treatment with Gemzar due to cardiovascular events such as myocardial infarction, cerebrovascular accident, arrhythmia, and hypertension. Many of these patients had a prior history of cardiovascular disease.

6.3 Adverse Event List for Docetaxel

Docetaxel 100 mg/m^2: Adverse drug reactions occurring in at least 5% of patients are compared for three populations who received docetaxel administered at 100 mg/m^2 as a 1-hour infusion every 3 weeks. The safety profile is generally similar in patients receiving docetaxel for the treatment of breast cancer and in patients with other tumor types.

6.3.1 Hematologic Reactions

Reversible marrow suppression was the major dose-limiting toxicity of docetaxel. The median time to nadir was 7 days, while the median duration of severe neutropenia (<500 cells/mm^3) was 7 days. Among 2045 patients with solid tumors and normal baseline LFTs, severe neutropenia occurred in 75.4% and lasted for more than 7 days in 2.9% of cycles. Febrile neutropenia (<500 cells/mm^3 with fever >38°C with intravenous antibiotics and/or hospitalization) occurred in 11% of patients with solid tumors, in 12.3% of patients with metastatic breast cancer, and in 9.8% of 92 breast cancer patients premedicated with 3-day corticosteroids. Severe infectious episodes occurred in 6.1% of patients with solid tumors, in 6.4% of patients with metastatic breast cancer, and in 5.4% of 92 breast cancer patients premedicated with 3-day corticosteroids. Thrombocytopenia (<100,000 cells/mm^3) associated with fatal gastrointestinal hemorrhage has been reported.

6.3.2 Hypersensitivity Reactions

Severe hypersensitivity reactions have been reported. Minor events, including flushing, rash with or without pruritus, chest tightness, back pain, dyspnea, drug fever, or chills, have been reported and resolved after discontinuing the infusion and instituting appropriate treatment.

6.3.3 Fluid Retention

Fluid retention can occur with the use of docetaxel.

6.3.4 Cutaneous Reactions

Severe skin toxicity is discussed elsewhere in the label. Reversible cutaneous reactions characterized by a rash including localized eruptions, mainly on the feet and/or hands, but also on the arms, face, or thorax, usually associated with pruritus, have been observed. Eruptions generally occurred within 1 week after docetaxel infusion, recovered before the next infusion, and were not disabling. Severe nail disorders were characterized by hypo- or hyperpigmentation, and occasionally by onycholysis (in 0.8% of patients with solid tumors) and pain.

6.3.5 Neurologic Reactions

Neurologic reactions are discussed elsewhere in the label.

6.3.6 Gastrointestinal Reactions

Nausea, vomiting, and diarrhea were generally mild to moderate. Severe reactions occurred in 3-5% of patients with solid tumors and to a similar extent among metastatic breast cancer patients. The incidence of severe reactions was 1% or less for the 92 breast cancer patients premedicated with 3-day corticosteroids. Severe stomatitis occurred in 5.5% of patients with solid tumors, in 7.4% of patients with metastatic breast cancer, and in 1.1% of the 92 breast cancer patients premedicated with 3-day corticosteroids.

6.3.7 Cardiovascular Reactions

Hypotension occurred in 2.8% of patients with solid tumors; 1.2% required treatment. Clinically meaningful events such as heart failure, sinus tachycardia, atrial flutter, dysrhythmia, unstable angina, pulmonary edema, and hypertension occurred rarely. Seven of 86 (8.1%) of metastatic breast cancer patients receiving docetaxel 100 mg/m^2 in a randomized trial and who had serial left ventricular ejection fractions assessed developed deterioration of LVEF by ≥10% associated with a drop below the institutional lower limit of normal.

6.3.8 Infusion Site Reactions

Infusion site reactions were generally mild and consisted of hyperpigmentation, inflammation, redness or dryness of the skin, phlebitis, extravasation, or swelling of the vein.

6.3.9 Hepatic Reactions

In patients with normal LFTs at baseline, bilirubin values greater than the ULN occurred in 8.9% of patients. Increases in AST or ALT >1.5 times the ULN, or alkaline phosphatase >2.5 times ULN, were observed in 18.9% and 7.3% of patients, respectively. While on docetaxel, increases in AST and/or ALT >1.5 times ULN concomitant with alkaline phosphatase >2.5 times ULN occurred in 4.3% of patients with normal LFTs at baseline. Whether these

changes were related to the drug or underlying disease has not been established.

7. PHARMACEUTICAL INFORMATION

7.1 Vorinostat (ZOLINZA)

Vorinostat capsules, 100 mg, are white, opaque hard gelatin capsules with “568” over “100 mg” printed within the radial bar in black ink on the capsule body. They are supplied as follows:

NDC 0006-0568-40.

Each bottle contains 120 capsules.

7.1.1 Storage and Handling

Store at 20-25°C (68-77°F), excursions permitted between 15-30°C (59-86°F). [See USP Controlled Room Temperature]

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published.[1-5] There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

Vorinostat capsules should not be opened or crushed. 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.

7.1.2 Instructions

Patients should be instructed to drink at least 2 liter/day of fluid to prevent dehydration and should promptly report excessive vomiting or diarrhea to their physician. Patients should be instructed about the signs of deep vein thrombosis and should consult their physician should any evidence of deep vein thrombosis develop. Patients receiving vorinostat should seek immediate medical attention if unusual bleeding occurs. Vorinostat capsules should not be opened or crushed.

7.2 Gemcitabine (Gemzar)

7.2.1 How Supplied

Gemcitabine (for injection, USP), is available in sterile single-use vials individually packaged in a carton containing:

Two hundred (200) mg white to off-white, lyophilized powder in a 10-mL size sterile single-use vial - NDC 0002-7501-01 (No. 7501)

One (1) g white to off-white, lyophilized powder in a 50-mL size sterile single-use vial - NDC 0002-7502-01 (No. 7502)

7.2.2 Storage and Handling

Unopened vials of gemcitabine are stable until the expiration date indicated on the package when stored at controlled room temperature 20° to 25°C (68° to 77°F) and that allows for excursions between 15° and 30°C (59° and 86°F).

7.2.3 Preparation and Administration

The recommended diluent for reconstitution of gemcitabine is 0.9% sodium chloride injection without preservatives. Due to solubility considerations, the maximum concentration for gemcitabine upon reconstitution is 40 mg/mL. Reconstitution at concentrations greater than 40 mg/mL may result in incomplete dissolution, and should be avoided.

To reconstitute, add 5 mL of 0.9% sodium chloride injection to the 200-mg vial or 25 mL of 0.9% sodium chloride injection to the 1-g vial. Shake to dissolve. These dilutions each yield a gemcitabine concentration of 38 mg/mL which includes accounting for the displacement volume of the lyophilized powder (0.26 mL for the 200-mg vial or 1.3 mL for the 1-g vial). The total volume upon reconstitution will be 5.26 mL or 26.3 mL, respectively. Complete withdrawal of the vial contents will provide 200 mg or 1 g of gemcitabine, respectively. Prior to administration the appropriate amount of drug must be diluted with 0.9% sodium chloride injection. Final concentrations may be as low as 0.1 mg/mL. Reconstituted gemcitabine is a clear, colorless to light straw-colored solution. After reconstitution with 0.9% sodium chloride Injection, the pH of the resulting solution lies in the range of 2.7 to 3.3. The solution should be inspected visually for particulate matter and discoloration prior to administration, whenever solution, or container, permit. If particulate matter or discoloration is found, do not administer.

When prepared as directed, gemcitabine solutions are stable for 24 hours at controlled room temperature 20° to 25°C (68° to 77°F). Discard unused portion. Solutions of reconstituted gemcitabine should not be refrigerated, as crystallization may occur. The compatibility of gemcitabine with other drugs has not been studied. No incompatibilities have been observed with infusion bottles or polyvinyl chloride bags and administration sets.

Gemcitabine will be administered at a fixed dose rate infusion at 10 mg/m^2/min.

7.3 Docetaxel

Docetaxel injection is a cytotoxic anticancer drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing docetaxel injection solutions. The use of gloves is recommended.

If docetaxel injection or diluted solution for intravenous infusion should come into contact with the skin, immediately, and thoroughly wash with soap and water. If docetaxel injection or diluted solution for intravenous infusion should come into contact with mucosa,

immediately and thoroughly wash with water.

Contact of the docetaxel injection with plasticized PVC equipment or devices used to prepare solutions for infusion is not recommended. In order to minimize patient exposure to the plasticizer DEHP (di-2-ethylhexyl phthalate), which may be leached from PVC infusion bags or sets, the final docetaxel injection dilution for infusion should be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Docetaxel injection requires dilution prior to administration. Please follow the preparation instructions provided below.

7.3.1 Preparation and Administration

Docetaxel injection (10 mg/mL) requires NO prior dilution with a diluent and is ready to add to the infusion solution.

Dilution for infusion

1. Aseptically withdraw the required amount of docetaxel injection solution (10 mg docetaxel/mL) with a calibrated syringe and inject into a 250 mL infusion bag or bottle of either 0.9% sodium chloride solution or 5% dextrose solution to produce a final concentration of 0.3 to 0.74 mg/mL.
2. If a dose greater than 200 mg of docetaxel injection is required, use a larger volume of the infusion vehicle so that a concentration of 0.74 mg/mL docetaxel injection is not exceeded.
3. Thoroughly mix the infusion by manual rotation.
4. As with all parenteral products, docetaxel injection should be inspected visually for particulate matter or discoloration prior to administration whenever the solution and container permit. If the docetaxel injection or diluted solution is not clear or appears to have precipitation, these should be discarded.
5. The docetaxel injection diluted solution for infusion should be administered intravenously as a 1-hour infusion under ambient room temperature below 25ºC (77ºF) and lighting conditions.

7.3.2 Stability

Docetaxel injection infusion solution, if stored between 2°C and 25°C (36°F and 77°F) is stable for 4 hours in either 0.9% sodium chloride solution or 5% dextrose solution. Use within 4 hours including the 1 hour intravenous administration. Do not freeze infusion solution.

Docetaxel injection 10 mg/mL is supplied as 20 mg/2 mL, 80 mg/8 mL and 160 mg/16 mL.

Each mL of docetaxel injection contains 10 mg docetaxel; 80 mg polysorbate 80; 648 mg polyethylene glycol 300; 275.9 mg alcohol 96% (v/v), and 4 mg citric acid.

8. CORRELATIVE/SPECIAL STUDIES

8.1 Pharmacokinetics

8.1.1 Sampling

To characterize the pharmacokinetics of single-agent vorinostat, blood samples will be drawn prior to starting the study treatment and on day 1.

Pharmacokinetic studies will be done during the first cycle on all patients on the Phase 1 portion and for the first 6-9 patients on the Phase 2 portion (to have at least 12 patients on the MTD/Recommended Phase 2 Dose). Patients will have blood samples drawn on day -1 to characterize the pharmacokinetics of single-agent vorinostat. Blood samples will be drawn on day 8 to characterize the pharmacokinetics of vorinostat and gem/tax given in combination. On day -1, 5 mL of blood will be collected in a redtop vacutainer tube (without anticoagulant; Becton Dickinson) before and at 0.5, 1, 1.5, 2, 3, 4, 6, and 24 h after ingestion of vorinostat. On day 8, samples will be collected before and at 0.5, 1, 1.5, 2, 3, 4, 6, and 24 h after ingestion of vorinostat. All time points can be performed within a window of +/- 10 minutes except for the 6 h and 24 h which will have a window of +/- 60 minutes.

8.1.2 Analytic chemical methods

Concentrations of vorinostat will be quantitated with a liquid chromatography-electrospray ionization tandem mass spectrometric method that was developed and validated at our institution (18).

8.2 Pharmacodynamics

Pharmacodynamic sampling will be performed on all accrued patients. During each cycle on days 1 (pre- and post- drug administration- end of gemcitabine infusion) and 8 (pre- and post- drug administration-end of docetaxel infusion) whole blood will be collected and processed to isolate peripheral blood mononuclear cells (PBMC). In cycle 1, PD samples will be collected on day -1 (pre- and post-drug administration- vorinostat).

Fine needle aspirates (FNA) and/or core biopsies of tumor samples will be obtained from consenting patients with accessible, evaluable disease, pre-treatment (before first dose of vorinostat) and on day 8 (after the 3 drugs are administered) of the first cycle and when patients go off study. Biopsies are optional in Phase 1 and Phase 2 for all consenting subjects.

RNA and DNA will be extracted using appropriate extraction kits.

9. MEASUREMENT OF EFFECT

For the purposes of this study, patients should be re-evaluated every 6 weeks. In addition to a baseline scan, confirmatory scans will also be obtained at least 4 weeks following initial documentation of an objective response.

9.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks. In addition to a baseline scan, confirmatory scans should also be obtained not less than 4 weeks following initial documentation of objective response.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

9.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment.

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of treatment, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

9.1.2 Disease Parameters

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

Note: Tumor lesions that are situated in a previously irradiated area will be considered measurable if there has been evidence of progression in those lesions since the last course of radiation treatment.

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.

Non-measurable disease. All other lesions (or sites of disease), including small lesions

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

9.1.3 Methods 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.

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

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

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

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

9.1.4 Response Criteria

9.1.4.1 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 progressions).

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.

9.1.4.2 Evaluation of Non-Target Lesions

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

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

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

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

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

9.1.4.3 Evaluation of Best Overall Response

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

Table 12. For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not	No	SD	Documented at least once ≥4 wks. from baseline**

	evaluated			
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** Only for non-randomized trials with response as primary endpoint.

*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

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

Table 13. For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)

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

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

9.1.5 Duration of Response

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

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

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

9.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design

10.1.1 Phase 1b

The Phase 1 portion of the study follows a standard "3+3" Phase 1 design in which gemcitabine and docetaxel will be given at a fixed dose while vorinostat will be dose-escalated as shown in Table 3. Gemcitabine will be given on days 1 and 8 at 900 mg/m^2 IV over 90 minutes and docetaxel will be given at 75 mg/m^2 IV over 60 minutes on day 8 every 21 days. Vorinostat will be given orally at the specified dose levels (Table 2) on days -1 (or day 21 of the previous cycle for all subsequent cycles) to +2 and days +7-9 every 21 days (treatment for 3 days starting one day prior to chemotreatment). Only DLTs observed in a patient during the first cycle will be used for the dose escalation decision. At MTD, an extension cohort of 6 will be accrued to better characterize the toxicity profile of the combination. Patients will be started on dose level 1 but if unacceptable toxicity is observed then vorinostat dose will be de-escalated to dose level -1. If unacceptable toxicity is observed at dose level -1 we will explore dose level -2 in which vorinostat will be given at 200 mg PO qd but the Gem dose will be decreased to 675 mg/m^2 on days 1 and 8.

10.1.2 Phase 2

The recommended Phase 2 dose (RP2D) will be taken to the next portion of the trial which is a single arm open-label Phase 2 trial of Gem/Tax + vorinostat in patients with advanced sarcomas. Based on the SARC002 data for the combination of gemcitabine+docetaxel in which this was an active regimen and had a PFR at 3 months well-over 20%. The 6-months PFR is a more relevant clinical outcome for this combination and the addition of vorinostat should improve upon this and therefore chose a higher benchmark of 6-month PFR being 40% or higher considered as success.

We will employ Simon's Optimal two-stage design (22) to distinguish between a promising 6-month progression-free survival rate (PFR) of 40% and a discouraging PFR of 20% (based on Van Glabbeke et al. (6) and Maki et al. (7)): Initially, a total of 17 (12 from the phase 1b portion of this protocol) patients will be accrued. The study will be held till the last patient entered the study is followed for at least 6 months. We do not anticipate any loss-to-follow up to happen within 6 months in our study. To resume and continue to full accrual based on PFR, at least 4 out of the first 17 patients must be progression-free and alive at six months. If the study passes these interim conditions, additional 20 patients will be accrued. We will conclude that the regimen is promising and worth y of further study if at least 11/37 patients are alive and progression-free at six month. If the true 6-month RFR is 20% or less, we will

have at least 24% chance to stop the trial at the end of the first stage. The type I and II errors of the design are both 10%.

10.2 Sample Size/Accrual Rate

10.2.1 Phase 1b

This will be a standard "3+3" Phase 1 design in which Gem and Tax will be given at a fixed dose while vorinostat will be dose-escalated. Given 4 possible dose levels (at a maximum of 6 each) and an additional 6 on MTD expansion phase (RP2D), a minimum of 6 and a maximum of 30 patients may be enrolled.

10.2.2 Phase 2

The Phase 2 portion will be an open-label single arm Phase 2 clinical trial to determine the safety and efficacy of Gem/Tax in combination with vorinostat in patients with advanced sarcomas.

A maximum of 37 (12 carried over from the phase 1 portion of the protocol) patients will be accrued in the phase 2 portion of the trial. For the Phase 2 portion, at an accrual rate of approximately 20 pts/year, the phase 2 portion of the study will be completed in about 2 years.

10.3 Endpoints

10.3.1 Primary endpoints:

- Phase 1b: To determine the safety, tolerability, and Phase 2 recommended dose (RP2D) of the combination.
- Phase 2: Six-month progression-free survival rate (PFR).

10.3.2 Secondary endpoints:

- Progression-free survival (PFS)
- Overall survival (OS)
- Overall response rate (ORR) as determined by RECIST criteria.

10.3.3 Exploratory endpoints:

- Correlative endpoints
- DNA methylation measured by microarray
- Expression level of genes as measured by microarray

10.4 Statistical Analysis and Summaries

10.4.1 Demographics

Baseline descriptive statistics on all evaluable patients will be provided for demographic variable (age, sex, race/ethnicity), ECOG performance status, disease stage and status of the time of enrollment, and treatment regiments previously used.

10.4.2 Safety Analysis

The NCI common terminology criteria for adverse events (AE) (CTCAE 4.0) will be used to evaluate toxicity; we will consider a toxicity to be an adverse event that is possibly, probably or definitely related to treatment. The maximum grade of toxicity for each category of interest will be recorded for each patient and the summary results will be tabulated by category and grade, and by dose level, if warranted. If, during the phase II portion of the study, we observe toxicities that would have been classified as DLTs during the phase I portion, we will describe them on a patient-by-patient basis and will include any relevant baseline data, such as number and type of prior therapies. If such toxicities occur in more than 1/3 of the patients, we will consider a re-evaluation of the MTD.

10.4.3 Efficacy Analysis

The Kaplan-Meir plot of PFS on the phase 2 portion of the study will be provided with corresponding 95% confidence band. Six-month PFR and the corresponding 95% confidence interval (CI) will be calculated. Similar analysis will be carried out for the OS. The percentage of eligible and evaluable patients experiencing an objective response (complete response or partial response by RECIST criteria) will be reported along with the corresponding exact 95% confidence limits.

10.4.4 Pharmacokinetics Analysis

Plasma concentration versus time data for vorinostat and metabolites will be analyzed noncompartmentally using the PK solutions. The day 1-to-day 8 changes in vorinostat pharmacokinetic variables will be assessed via the Wilcoxon signed ranks test; two-sided P values will be reported.

10.4.5 Pharmacodynamics Analysis

The comparison of genetic profile and methylation profile before and after the treatment will be conducted similar to the work presented by our group (21). Briefly, paired t test (or non-parametric test) will be used to compare the expression level (or methylation level) before and after the treatment. The false discovery rate (FDR) will be controlled at 10% using the Benjamini and Hochberg's procedure (23). Clustering analysis will be used to explore the relationship between the markers that are modulated by the treatment. Pathway analysis will be used to explore the pathways that are modulated by the treatment.

11. DATA SAFETY MONITORING PLAN

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet monthly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues
- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria version 4.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue, or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPCI DSMC

which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, only need to be reviewed twice a year by the disease center DSMB.

Both the UPCI DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

12. ADVERSE EVENT REPORTING

12.1 Definitions

Adverse event: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Life-threatening adverse event or *life-threatening suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the investigator, its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

Serious adverse event or *serious suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

Suspected adverse reaction: Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Unexpected adverse event or *unexpected suspected adverse reaction:* An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

12.2 Review of Safety Information[1]

The investigator must promptly review all information relevant to the safety of the drug obtained or otherwise received by the investigator from foreign or domestic sources, including information derived from any clinical or epidemiological investigations, animal or in vitro studies, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities and reports of foreign commercial marketing experience for drugs that are not marketed in the United States.

12.3 Reporting adverse events to the responsible IRB and Supporter

In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) associated with the investigational drug or study treatment(s); 2) serious; and 3) unexpected. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the investigator's receipt of the respective information. Adverse events which are 1) associated with the investigational drug or study treatment(s); 2)

[1] 21 CFR Sec. 312.50

fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

Merck Sharp & Dohme Corp. [redacted] will be provided with copies of all serious adverse experiences regardless of causality to use of a Merck Product, within two working days. Additionally, any pregnancy occurring in association with use of a Merck Product will be reported to Merck Sharp & Dohme Corp. [redacted]. Serious adverse experience means any experience that suggest a significant hazard, contraindication, side effect or precaution. A serious adverse experience includes any experience that is fatal or immediately life threatening, results in a persistent or significant disability/incapacity, requires or prolongs in-patient hospitalization, or isa congenital anomaly, cancer, or overdose. Other important medical events that may not result in death, not be life-threatening, or not require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize thesubject/patient and may require medical or surgical intervention to prevent one of the outcomes listed previously.

13. QUALITY CONTROL AND QUALITY ASSURANCE

Independent monitoring of the clinical study for protocol and GCP compliance will be conducted periodically (i.e., at a minimum of annually) by qualified staff of the Education and Compliance Office – Human Subject Research, Research Conduct and Compliance Office, University of Pittsburgh.

The Investigator and the University of Pittsburgh and UPMC will permit direct access of the study monitors and appropriate regulatory authorities to the study data and to the corresponding source data and documents to verify the accuracy of this data.

14. DATA HANDLING AND RECORD-KEEPING

The Investigator will maintain records in accordance with Good Clinical Practice guidelines.

The Investigator will retain the specified records and reports for up to 2 years after the marketing application is approved for the investigational drug; or, if a marketing application is not submitted or approved for the investigational drug, until 2 years after investigations under the IND have been discontinued and the FDA so notified.

15. ETHICS

15.1 Institutional Review Board (IRB) approval

The Investigator will obtain, from the University of Pittsburgh Institutional Review Board (IRB), prospective approval of the clinical protocol and corresponding informed consent form(s); modifications to the clinical protocol and corresponding informed consent forms, and advertisements (i.e., directed at potential research subjects) for study recruitment.

The only circumstance in which a deviation from the current IRB-approved clinical protocol/consent form(s) may be initiated in the absence of prospective IRB approval is to eliminate an apparent immediate hazard to the research subject(s). In such circumstances, the Investigator will promptly notify the University of Pittsburgh IRB of the deviation.

The University of Pittsburgh IRB operates in compliance with FDA regulations at 21 CFR Parts 50 and 21 CFR 56, and in conformance with applicable International Conference on Harmonization (ICH) Guidelines on Good Clinical Practice (CGP).

In the event that the University of Pittsburgh IRB requires, as a condition of approval, substantial changes to a clinical protocol submitted under an FDA-accepted IND application, or in the event of the Investigator's decision to modify the previously accepted clinical protocol:

- for a Phase 1 clinical study: The Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to the Phase 1 clinical protocol that significantly affects the safety of the subjects. For changes that do not affect critical safety assessments, the revisions to the clinical protocol may be addressed in the Annual Report to the IND.
- for Phase 2 and 3 clinical studies: The Investigator will submit (i.e., in advance of implementing the change) a Protocol Amendment to the IND describing any change to a Phase 2 or Phase 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of Phase 2 and 3 clinical protocol changes requiring the submission of a Protocol Amendment include:
    - Any increase in drug dosage or duration of exposure of individual subjects to the investigational drug beyond that described in the current protocol, or any significant increase in the number of subjects under study.
    - Any significant change in the design of the protocol (such as the addition or deletion of a control group).
    - The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor the safety of the investigational drug.

15.2 Ethical and scientific conduct of the clinical research study

The clinical research study will be conducted in accordance with the current IRB-approved

clinical protocol; ICH GCP Guidelines adopted by the FDA; and relevant policies, requirements, and regulations of the University of Pittsburgh IRB, University of Pittsburgh and UPMC, Commonwealth of Pennsylvania, and applicable federal agencies.

15.3 Subject informed consent

The Investigator will make certain that an appropriate informed consent process is in place to ensure that potential research subjects, or their authorized representatives, are fully informed about the nature and objectives of the clinical study, the potential risks and benefits of study participation, and their rights as research subjects. The Investigator, or a sub-investigator(s) designated by the Investigator, will obtain the written, signed informed consent of each subject, or the subject's authorized representative, prior to performing any study-specific procedures on the subject. The date and time that the subject, or the subject's authorized representative, signs the informed consent form and a narrative of the issues discussed during the informed consent process will be documented in the subject's case history. The Investigator will retain the original copy of the signed informed consent form, and a copy will be provided to the subject, or to the subject's authorized representative.

The Investigator will make certain that appropriate processes and procedures are in place to ensure that ongoing questions and concerns of enrolled subjects are adequately addressed and that the subjects are informed of any new information that may affect their decision to continue participation in the clinical study. In the event of substantial changes to the clinical study or the risk-to-benefit ratio of study participation, the Investigator will obtain the informed consent of enrolled subjects for continued participation in the clinical study

16. REFERENCES

1. Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010, CA Cancer J Clin. 2010 Sep-Oct;60(5):277-300.
2. Yan JC, Glatstein E, Rosenberg SA, Antman DH, Sarcomas of soft tissues, in Cancer: Principles & Practice of Oncology, Fourth Ed. DeVita VT, Jr, Hellman S, Gosenberg SA (eds). JB Lippincott, Philadelphia, 1436-1488, 1993.
3. Borden EC, Arnato DA, Rosenbaum C, Enterline HT, Shiraki MJ, Creech RH, Lerner H-I, Carbone PP. Randomized comparisons of three adriamycin regimens for metastatic soft tissue sarcomas. J Clin Oncol 5:840-850, 1987.
4. Edmonson JH, Ryan LM, Blum RH, Brooks JSJ, Shiraki M, Frytak S, Parkinson DR. Randomized comparison of doxorubicin alone versus ifosfamide plus doxorubicin or mitomycin, doxorubicin, and cisplatin against advanced soft tissue sarcomas. J ClinOncol 11:1269-1275, 1993.
5. Antman K, Crowley J, Balcerzak SP, Rivkin SE, Weiss GR, Elias A, Natale RB, Cooper RM, Barlogie B, Trump DL, Doroshow JH, Aisner J, Pugh RP, Weiss RB, Cooper BA, Clamond GH, Baker LH. An Intergroup Phase II randomized study of doxorubicin and dacarbazine with or without ifosfamide and mesna in advanced soft tissue sarcomas. J Clin Oncol 11:1276-1285, 1993.

6. Van Glabbeke M, Verweij J, Judson I, Nielsen OS. Progression-free rate as the principal end-point for phase II trials in soft-tissue sarcomas. Eur J Cancer 38:543-549, 2002.
7. Maki RG, Wathen JK, Patel SR, Priebat DA, Okuno SH, Samuels B, Fanucchi M, Harmon DC, Schuetze SM, Reinke D, Thall PF, Benjamin RS, Baker LH, Hensley ML. Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study 002. J Clin Oncol. 2007 Jul 1;25(19):2755-63.
8. Zolinza® (vorinostat) Product Circular, www.fda.gov, August 23, 2011.
9. Gemzar® (gemcitabine) Product Circular, www.fda.gov, August 23, 2011.
10. Taxotere® (docetaxel) Product Circular, www.fda.gov, August 23, 2011.
11. Bay JO, Ray-Coquard I, et al. Docetaxel and gemcitabine combination in 133 advanced soft-tissue sarcomas: a retrospective analysis. Int J Cancer. 2006 Aug 1;119(3):706-11.
12. Esteller, M., *Cancer epigenomics: DNA methylomes and histone-modification maps*. Nat Rev Genet, 2007. **8**(4): p. 286-98.
13. Yoo, C.B. and P.A. Jones, *Epigentic treatment in cancer: Past, present and future*. Nat Rev Drug Discov, 2006. **5**(1): p. 37-50.
14. Johnstone, R.W., *Histone deacetylase inhibitors: Novel drugs for the treatment of cancer.* Nat Rev Drug Discov, 2002. **1**(4): p. 287-99.
15. Arnold NB, Arkus N, et al. *The histone deacetylase inhibitor suberoylanilide hydroxamic acid induces growth inhibition and enhances gemcitabine-induced cell death in pancreatic cancer*. Clin Cancer Res. 2007 Jan 1;13(1):18-26.
16. Rundall BK, Denlinger CE, Jones DR. *Suberoylanilide hydroxamic acid combined with gemcitabine enhances apoptosis in non-small cell lung cancer.* Surgery. 2005 Aug;138(2):360-7.
17. Owonikoko TK. , Ramalingam SS, et al. *Vorinostat increases carboplatin and paclitaxel activity in non-small cell lung cancer cells.* Int. J. Cancer: 126, 743–755 (2010).
18. Ramalingam SS, Parise RA, et al. *Phase I and pharmacokinetic study of vorinostat, a histone deacetylase inhibitor, in combination with carboplatin and paclitaxel for advanced solid malignancies*. Clin Cancer Res. 2007 Jun 15;13(12):3605-10.
19. Ramalingam SS, Maitland M, et al. *Carboplatin and Paclitaxel in combination with either vorinostat or placebo for first-line treatment of advanced non-small-cell lung cancer.* JCO 2010 Jan 1;28(1):56-62. Epub 2009 Nov 23.
20. Schneider BJ, Kalemkerian GP, Bradley D, Smith DC, Egorin MJ, Daignault S, Dunn R, Hussain M. Phase I study of vorinostat (suberoylanilide hydroxamic acid, NSC 701852) in combination with docetaxel in patients with advanced and relapsed solid malignancies. Invest New Drugs. 2010 Aug 5 [Epub ahead of print].
21. Tawbi H., Buch S., et al. *Prediction of response to alkylator-based chemotreatment in metastatic melanoma (MM) using gene expression and promoter methylation signatures.* ASCO 2009 Annual Meeting, Oral Presentation (Abstract # 9009).
22. Simon R: Optimal two-stage designs for phase II clinical trials. *Control Clin Trials* 1989, 10: 1-10.
23. Benjamini, Yoav; Hochberg, Yosef (1995). "Controlling the false discovery rate: a practical and powerful approach to multiple testing". *Journal of the Royal Statistical Society, Series B (Methodological)* **57** (1): 125–133.

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.