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Phase I Pharmacokinetic Study of Belinostat for Solid Tumors and Lymphomas in Patients with Varying Degrees of Hepatic Dysfunction

Abbreviated Title: PhI Belinostat ODWG

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Protocol Version Date: October 25, 2018

PRÉCIS

Background:

- Belinostat is a histone deacetylase (HDAC) inhibitor. HDACs are frequently deregulated in cancer cells, leading to an increase in deacetylation and the silencing of genes that normally control cell cycle arrest and apoptosis.
- Belinostat has growth inhibitory activity in several malignancies in vitro and in vivo, both as a single agent and in combination with chemotherapeutic agents. Several Phase I and II clinical trials have been conducted to date in patients with solid tumor and hematologic malignancies; belinostat has been generally well tolerated.
- Belinostat is metabolized in the liver and therefore, the safety and dosing of belinostat needs to be established in patients with varying degrees of hepatic dysfunction.

Objectives:

- Establish the safety and tolerability of belinostat given on days 1–5 of 21-day cycles to patients with varying degrees of liver dysfunction.
- Define the maximum tolerated dose (MTD) and recommended dose of belinostat given on days 1–5 of 21-day cycles to patients with varying degrees of liver dysfunction.
- Evaluate the pharmacokinetics (PK) of one dose of belinostat (400 mg/m^2) in patients with varying degrees of liver dysfunction
- Obtain preliminary evidence of anti-tumor activity at tolerable doses of belinostat in patients with varying degrees of liver dysfunction.
- Correlate observed toxicities with PK of belinostat in patients with varying degrees of liver dysfunction.
- Measure direct versus indirect bilirubin levels and correlate these with observed toxicities and PK.

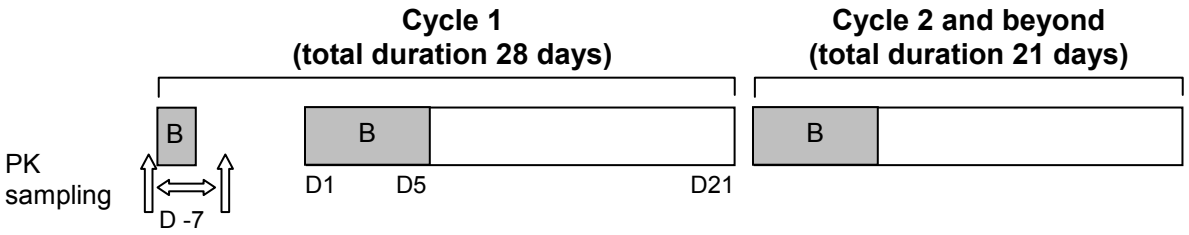
Eligibility:

- Adults with solid tumors or lymphomas whose disease has progressed after standard therapy or who have no acceptable standard treatment options. Patients with normal and varying degrees of hepatic dysfunction (mild, moderate, and severe) are eligible.

Study Design:

- Patients will be divided into 4 cohorts based on their level of liver dysfunction. Belinostat will be administered IV over 30 minutes. On day -7 (Cycle 1 only), all patients will receive a single dose of 400 mg/m^2 belinostat. On days 1–5 of each cycle, patients will receive belinostat at a dose dependent on the level of hepatic dysfunction (see below). The total length of Cycle 1 will be 28 days; all other cycles will be 21 days. No more than 12 patients with normal hepatic function will be accrued.

SCHEMA



B = Belinostat, administered IV over 30 minutes. On Day -7 (Cycle 1 only), **all patients** will receive a single dose of 400 mg/m^2 belinostat.

Starting on Day 1, patients will receive the assigned dose of belinostat, according to the dose escalation scheme, for Days 1–5 of each cycle.

Blood samples for correlative PK studies will be collected from all patients on Cycle 1 D-7 before the administration of belinostat, 15 minutes after starting infusion, and then at the following time points after the end of infusion: 5, 10, 15, 30, 60, 90 minutes, 2, 4, 6, 8, and 24 hours

Liver Dysfunction Groups

Cohort 1: Normal hepatic function: bilirubin ≤ upper limit of normal (ULN) **and** AST ≤ ULN

Cohort 2: **Mild hepatic dysfunction**: bilirubin > ULN but ≤ 1.5 x ULN **and/or** AST > ULN

Cohort 3: Moderate hepatic dysfunction: bilirubin > 1.5 x ULN to ≤ 3 x ULN and any AST

Cohort 4: Severe hepatic dysfunction: bilirubin > 3 x ULN but ≤ 10 x ULN and any AST

Dose Escalation Scheme

Dose Level of Belinostat (mg/m^2/day)

	-1	**1**	**2**	**3**	**4**
Cohorts: Normal	750	1000	No escalation	No escalation	No escalation
Mild Dysfunction	500	750	1000	No escalation	No escalation
Moderate Dysfunction	250	500	750	1000	No escalation
Severe Dysfunction	125	250	350	500	750

The initial cohorts of patients will begin on dose level 1 based on their level of hepatic dysfunction. Patients with normal hepatic function will not have their dose escalated.

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1.1.2 Define the maximum tolerated dose (MTD) and recommended dose of belinostat given on days 1–5 of 21-day cycles to patients with varying degrees of liver dysfunction.

1.1.3 Evaluate the pharmacokinetics (PK) of one dose of belinostat (400 mg/m^2) in patients with varying degrees of liver dysfunction.

1.2 Secondary Objectives

1.2.1 Obtain preliminary evidence of anti-tumor activity at tolerable doses of belinostat in patients with varying degrees of liver dysfunction.

1.2.2 Correlate observed toxicities with PK of belinostat in patients with varying degrees of liver dysfunction.

1.2.3 Measure direct versus indirect bilirubin levels and correlate these with observed toxicities and PK.

2 BACKGROUND

2.1 Belinostat

Belinostat (N-hydroxy-3-[phenylsulphamoylphenyl] acryl amide) is a novel, achiral, low molecular weight inhibitor of histone deacetylase (HDAC) activity.[1-3] The structural design of belinostat was based on natural products that were known inhibitors of HDAC.[4] It contains a zinc-chelating hydroxamic acid moiety that contributes to high levels of potency similar to other low molecular weight HDAC inhibitors, such as trichostatin A (TSA), oxamflatin, and suberoylanilide hydroxamic acid (SAHA).[5] Molecular modeling studies predict that belinostat binds within the active sites of HDAC class I and II enzymes, in a similar manner to that described for TSA and SAHA.[6, 7]

Mechanism of Action

HDACs exert their action during post-translational acetylation of core nucleosomal histones, which affects chromatin structure and thus regulates gene expression. Acetylation and deacetylation of histones is controlled by the activity of histone acetyltransferases (HATs) and HDACs. Acetylation of the e-amino groups of lysine residues in the N-terminal tails of histones is associated with transcriptional activation, while deacetylation is associated with condensation of chromatin and transcriptional repression. HDAC inhibitors, such as the natural product TSA and SAHA, induce the expression of genes associated with cell cycle arrest and tumor

suppression.[8-10] Phenotypic changes induced by HDAC inhibitors include G1 and G2/M cell cycle arrest and apoptosis in tumor cells. There are also data to suggest that HDAC inhibitors possess antiangiogenic properties. HDAC inhibitors deplete vascular endothelial cell growth factor (VEGF) concentrations and inhibit the proliferation of endothelial cells.[11]

DNA methylation and hypoacetylation of core nucleosome histone proteins leads to the tight coiling of chromatin, thus silencing the expression of a variety of genes.[12] HDAC inhibitors alone or in combination with DNA hypomethylating agents, such as 5-azacytidine or decitabine, restore expression of silenced genes, leading to cell differentiation and subsequent cell cycle arrest or apoptosis. Reports also suggest that HDAC inhibitors repress some genes, e.g., the gene for thymidylate synthetase, which may explain the reports of synergistic interaction between 5-FU and these inhibitors.[13, 14] Gene expression analyses with human HL-60 promyelocytic leukemia cells and HCT116 colon cancer cells, after exposure to belinostat (1 μM), TSA (1 μM), or FK228 (10 nM) suggest that belinostat may have similar gene induction and repression effects as other HDAC inhibitors (Investigator communication). HDAC inhibition also depleted the levels of several oncoproteins that are normally stabilized by binding to the 90 kD heat shock protein (Hsp90) in cancer cells, e.g., mutant p53 and Raf-1 proteins.[15] Concurrent administration of marginally toxic concentrations of 17-AAG, an Hsp90 inhibitor, with sublethal concentrations of HDAC inhibitors resulted in synergistic induction of apoptosis.[16]

Nonclinical Activity

Belinostat induced a concentration-dependent increase in acetylation of histones H3 and H4 in various tumor cell lines (ovarian, colon, lung, breast, prostate, and melanoma), with IC_{50} values varying from about 10 to 100 nM.[2, 17] In these same tumor cell lines, belinostat induced apoptosis or was cytotoxic with IC_{50} values varying from 0.2 to 3.4 μM.[2, 3, 7] Activity against the NCI 60 cancer panel is included as Appendix A. Other human tumor cell lines reported to be sensitive to belinostat are T-cell leukemia (Jurkat); small cell lung cancer (SCLC) (H69, GLC2, and GLC4); and multiple myeloma (JNN-2, LP-1, RPMI-8226, and U-266).[3,7] Belinostat also has activity in preclinical models of hepatocellular carcinoma (HCC), especially in combination with sorafenib. HDAC inhibitors have been shown to restore sensitivity to sorafenib in sorafenib-resistant HCC cell lines.

The antitumor activity of belinostat was demonstrated in several *in vivo* xenograft models, including human A2780 ovarian cancer cells, cisplatin-resistant A2780/cp70 ovarian cancer cells, HCT116 colon cancer cells, and murine P388 leukemia cells. Tumor-bearing mice were treated intraperitoneally (IP) with belinostat once daily for 7 days. Delay of tumor growth was observed at a dose of 10 mg/kg/day in A2780 and A2780/cp70 xenografts. Growth delay was dose dependent up to a belinostat dose of 40 mg/kg/day. Growth inhibition was also observed in xenografts of HCT116 cells at 40 mg/kg/day. Belinostat treatment did not affect body weight of the mice, nor were there apparent signs of toxicity. Hyperacetylated histone H4 was detected in peripheral blood mononuclear cells (PBMC) at 1 and 2 hours after a single IP injection of 40 mg/kg belinostat,[2] and acetylation returned to baseline levels by 3 hours. Histone hyperacetylation was dose dependent, with marked acetylation in both PBMCs and tumor tissue apparent at doses of belinostat ≥ 10 mg/kg.

The efficacy of various schedules of belinostat was evaluated in the murine P388 leukemia IP tumor model.[7] A schedule of 40 mg/kg/day × 5 days (from day 3) proved superior to the same total dose (200 mg/kg) administered in a bolus on day 3 ($P < 0.0001$). Fractionation of the daily dose (20, 40, or 80 mg/kg for 5 days) into two doses per day instead of one daily dose did not improve survival. Mice given a cumulative dose of 200 mg/kg over a 10-day period (day 3 to day 12) fractionated as 20 mg/kg/day for 10 days exhibited better survival than mice receiving 40 mg/kg every two days (day 3, 5, 7, 9, 11) ($P = 0.009$). Treatment every second day three times was compared with the same cumulative dose of 270 mg/kg belinostat administered every day in a 5-day period (day 3 to 7), and no significant differences were found in survival rates ($P = 0.49$). In general, daily doses appeared to be superior to bolus injections; fractionation of the daily dose into two did not result in any advantage; and experiments comparing alternating day to daily treatments favored the daily treatment, but not substantially.

Nonclinical Pharmacology and Toxicology

Due to the low intrinsic aqueous solubility of belinostat, the early *in vivo* studies were primarily carried out using a co-solvent formulation of ethanol and polyethylene glycol fractions (PEG) in Tris buffer (known as the co-solvent-Tris formulation).[7] However, this preparation proved unsuitable due to injection site reactions, and a new formulation was developed, which utilized the solubility-enhancing effects of arginine and led to the identification of the belinostat 50 mg/mL injection formulation. The *in vitro* studies were carried out using belinostat in a final concentration of < 1% DMSO, while the *in vivo* studies used the new injection formulation, after demonstration of bioequivalence.

The cardiovascular effects of belinostat were examined in dogs. The high dose (35 mg/kg) of belinostat elicited a small transient increase in heart rate.[7] Anticipated changes in the electrocardiogram waveform—such as decrease in the RR, PR, and QT intervals—were also observed. However, these changes were not substantially different from the control group. Increases in the rate of respiration following administration of the intermediate (15 mg/kg) and the high (35 mg/kg) doses of belinostat were not significantly different from those observed with the control group. The hemolytic potential and plasma compatibility of belinostat (in the arginine formulation) in human blood were examined ex vivo. No hemolysis was detected.

Pharmacokinetic (PK) studies were undertaken in mice, rats, and dogs.[7] The majority of the metabolite-profiling studies, coupled with preliminary investigation of excretion routes, were undertaken in rats and dogs. Plasma concentrations of belinostat in mice, determined after a single IP injection of 20 mg/kg, reached a mean concentration of 3.3 ± 0.7 μM after 0.5 hour, and decreased to 0.042 ± 0.002 μM by 2 hours. In general, the C_{max} was achieved at the first time point after the end of infusion and increased with dose. It then declined very rapidly with a $t_{1/2}$ of 0.5 to 1 hour. With daily administration, $t_{1/2}$ did not vary from day 1 to day 5. With few exceptions, the PK parameters did not vary from day 1 to day 5 (or 7) of a treatment cycle and did not vary from cycle 1 to cycle 2 where two cycles were administered over 4 weeks. There was no clear indication of drug accumulation following 5 or 7 days of treatment. Acetylation of histones H3 and H4 was also determined in canine PBMCs taken at various times after a 45-minute

intravenous (IV) infusion of 50 mg/kg belinostat.[2] At the end of the infusion, the plasma concentration of belinostat was between 20 and 30 μM, and the plasma $t_{1/2}$ was estimated at approximately 40 minutes.

In an exploratory *in vivo* study, metabolic profiling was undertaken in pooled samples from mouse, rat, and dog plasma following administration of belinostat. The study suggested that rapid and extensive metabolism took place, producing a variety of metabolites that differed in rodents and dogs. Since there was no consistency of either dose or sampling time, no further conclusions could be drawn. The overall metabolic profile observed in the two species appeared to be similar. The principal degradation product and a secondary metabolite were tested in the HDAC biochemical and cell proliferation assays and found to be inactive. Elimination of belinostat and its metabolites occurred by both urinary and fecal routes in both rats and dogs. Concentrations of parent drug cleared by either route were low when calculated as a percentage of the original dose, implying that the bulk of parent drug is cleared following primary and secondary metabolic conversion.

Toxicology studies were performed with both formulations of belinostat. Overall, in rats, the maximum tolerated dose (MTD) was considered to be between 100 and 200 mg/kg/day. Due to local irritation at injection sites, it was not possible to assign a no-observable-effect-level (NOEL) in rats. Systemic effects, however, even at the 100 mg/kg/day level, were mild with both formulations. Signs of local irritation at the injection sites with both formulations were observed in dogs as well, although a NOEL of 10 mg/kg/day was assigned in one study. Systemic and local irritation adverse events (AEs), such as lymphopenia, lymphoid atrophy, and injection site reactions, were observed at a dose of 50 mg/kg/day, but these were considered mild and fully reversible for the arginine formulation.

The potential for drug interactions of belinostat was determined *in vitro* in CYP inhibition, induction, and metabolism studies. Results indicate that belinostat is a weak/moderate inhibitor of CYP2C8 and CYP2C9, and may be a weak inducer of CYP1A2. CYP3A4 appears to contribute to the metabolism of belinostat; CYP isoforms are not responsible for the formation of the two major metabolites in humans.[7]

Phase I/II Clinical Experience

TopoTarget and the NCI have conducted 22 clinical trials to evaluate the IV formulation of belinostat alone and in combination with approved chemotherapeutic agents, including 5-FU, carboplatin and paclitaxel, doxorubicin, idarubicin, bortezomib, 5-azacytidine, 13-cis-retinoic acid, and dexamethasone. A total of 529 patients with advanced solid tumors and hematologic malignancies have been accrued as of January 2009; there is also one ongoing trial of the single-agent oral formulation (101 patients). Multiple dosing schedules are being investigated in these studies (Table 1; data from Investigators Brochure, and specified references). A dose of 1000 mg/m^2/day IV over 30 minutes on days 1–5 in a 21-day cycle is the most widely recommended Phase II dose.[3, 18-20]

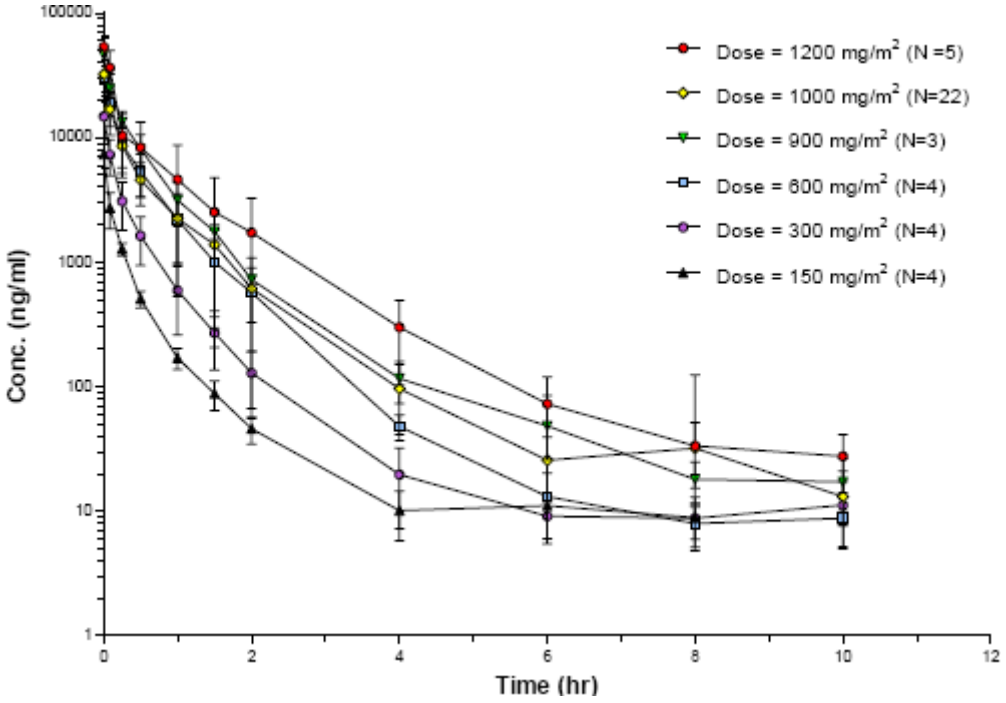
Table 1: Doses and Schedules Used for Clinical Administration of Belinostat by IV Infusion

Belinostat monotherapy	The recommended Phase II dose established in the initial Phase I study in patients with solid tumors is 1000 mg/m²/day by 30-minute intravenous infusion once daily on days 1-5 of a 21-day cycle.[19]
	The same recommended Phase II dose has also proved to be tolerated in patients with hematological malignancies.[18]
	An alternative recommended Phase II dose has been established in an NCI-sponsored Phase I study including patients with hepatocellular carcinoma. The Phase II dose used is 1400 mg/m²/day by 30-minute intravenous infusion once daily on days 1-5 of a 21-day cycle.
	Evaluation of a 48-hour belinostat monotherapy continuous infusion administered every 2 weeks is part of an ongoing Phase Ib study (800 mg/m²/24h for 48 hours as monotherapy, and 1000 mg/m²/24h for 48 hours has been applied in combination with idarubicin).
Belinostat in combination with other antitumor therapies	The recommended schedule of belinostat in combination with 5-FU is belinostat 1000 mg/m²/day by 30-min infusions once daily days 1-5 every 21 days in combination with 5-FU 750 mg/m²/24h by a 96-hour continuous infusion starting day 2.
	The recommended schedule of belinostat in combination with carboplatin and paclitaxel is 1000 mg/m²/day by 30-minute intravenous infusion once daily days 1-5 every 21 days, in combination with paclitaxel 175 mg/m² (started 2-3 hours after end of belinostat infusion on day 3) and carboplatin AUC 5 (chrome-EDTA clearance estimated GFR; following immediately after delivery of paclitaxel on day 3).
	The combination of belinostat with carboplatin and paclitaxel using an infusion time of up to 6 hours for belinostat rather than 30 minutes has been shown to be generally well tolerated.
	The recommended schedule of belinostat in combination with dexamethasone for patients with multiple myeloma is 1000 mg/m²/day by 30-minute intravenous infusion once daily days 1-5 every 21 days, in combination with dexamethasone administered orally (40 mg daily on cycle days 2-5 and 10-13).

Clinical benefit has been reported from both monotherapy and combination therapy with belinostat in solid and hematologic malignancies. Durable complete responses have been seen in patients with peripheral and cutaneous T-cell lymphoma; patients with peripheral T-cell lymphomas have also had persistent complete responses (CRs), and patients with multiple myeloma have had stable disease with belinostat alone. Belinostat combination therapy including carboplatin and paclitaxel has shown encouraging activity in previously treated patients with different types of solid tumors, including platinum-resistant ovarian cancer and transitional cell carcinoma of the bladder. Ovarian cancer patients (platinum-sensitive and platinum-resistant) treated with belinostat in combination with paclitaxel and carboplatin had CRs, partial responses (PRs), and a progression-free survival of 5.4 months; a CR and PRs were reported in patients with transitional cell bladder cancers. The combination of dexamethasone with belinostat in patients with myeloma has resulted in PRs, objective responses, and stable disease. Complete remissions were seen in patients with refractory acute myelogenous leukemia in combination with idarubicin. Long periods of stabilization have been seen in patients with thymoma and soft tissue sarcomas.

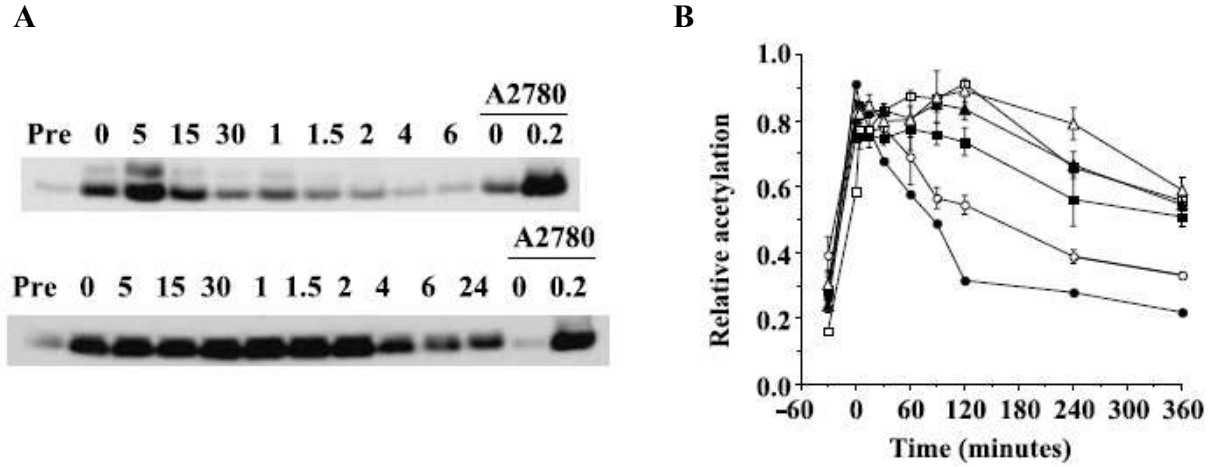
PK and pharmacodynamic (PD) information for belinostat has been obtained. The mean half-life is 0.6-2 hours. Most of the drug is out of the system within 8-10 hours after administration of 1000 mg/m^2 IV over 30 minutes. The PK for Cmax and AUC were linear with varying doses (Fig. 1). AUC and elimination were not affected by height, weight, age, or gender.

Fig. 1 Pharmacokinetic Data of Belinostat (150-1200 mg/m^2 IV) Derived From the Phase I Study in Patients With Solid Tumors



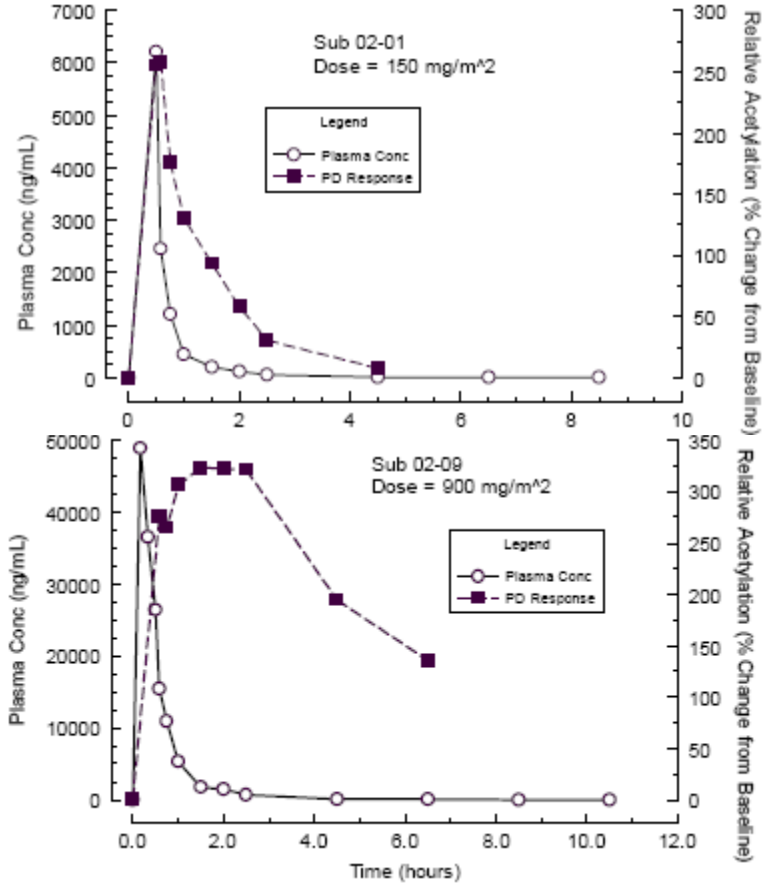
As a correlative PD study, changes in levels of histone H3 and H4 acetylation in patient PBMCs were also measured by Western blot following drug administration. As illustrated in Fig. 2, histone H4 hyperacetylation was sustained for 4-24 hours, despite the rapid decreases in drug concentration measured in Fig. 1. The level and the duration of histone acetylation were dose dependent, but approached plateaus by the MTD (Fig. 3; data from 2 representative patients in Fig. 2A). This would suggest that the maximum effect on the tumor can be achieved at the MTD; however, it is unclear if the acetylation in human PBMCs correlates with effect on tumor.

Fig. 2 Changes in PBMC Protein Histone H4 Acetylation Before and After Belinostat Administration in Patients With Solid Tumors



A: Western blot showing histone H4 acetylation in PBMC extract for 2 patients treated with belinostat (150 and 900 mg/m^2, respectively) pre-dose, and at defined time points afterward (5, 15, 30, 60, 90, 120 minutes, 4, 6, and 24 hours). B: Mean (+/- SE) for each dose: ●, 150mg/m^2 (n = 2) or 300 mg/m^2 (n = 4); ■, 600 mg/m^2 (n = 4); □, 900 mg/m^2 (n = 2); ▲ 1000 mg/m^2 (n = 11); ◊, 1200 mg/m^2 (n = 4).

Fig. 3 PK/PD Relationship for Belinostat in Patients With Solid Tumors



Relationship between relative histone H4 acetylation in PBMCs and belinostat plasma concentration in 2 patients receiving single 150 mg/m^2 (top) and 900 mg/m^2 (bottom) doses.

Based on information received to date, belinostat has been generally well tolerated. The most common side effects of any grade have been nausea, vomiting, and fatigue, and the most frequent grade 3/4 event has been fatigue.[7]

Serious AEs (SAEs) have been reported in 225 of the 420 patients exposed to belinostat in all clinical trials. The most frequent SAEs (reported in more than 2% of patients receiving IV belinostat irrespective of causal relationship) were disease progression (5.6%), febrile neutropenia (3.8%), infection (4.1%), pneumonia (2.5%), dyspnea (2.2%), and pyrexia (3.2%). The Comprehensive Adverse Event and Potential Risks (CAEPR) list for belinostat is included in Section 7.1.

Out of 420 patients who received belinostat in studies conducted by TopoTarget, 7 cardiotoxicities were attributed to the drug (2 atrial fibrillation events, 1 tachycardia, 1 ventricular fibrillation, 1 chest pain, 1 angina pectoris, and 1 myocardial ischemia). It is not clear whether these events were incidental in a group at high risk or if they were from the drug; however, specific exclusionary criteria regarding preexisting cardiac conditions and dose modifications if any events occur while on therapy are included in this protocol.

Study Considerations

There may be interactions with drugs that also affect CYP 450, especially CYP 2C9, which includes Coumadin. Forty-one patients on Coumadin have received belinostat. From what is known to date, warfarin is not contraindicated, but should be monitored.

Cytopenias were a rare and minor when belinostat is given as a single agent, though severe AEs were seen when it was used in combination with cytotoxic chemotherapy.

2.2 Rationale

Belinostat looks promising for the treatment of patients with cancer, having activity in several malignancies as monotherapy and in combination. Exploring appropriate dosing for patients with varying degrees of hepatic dysfunction would be beneficial for patients with many malignancies. Belinostat is metabolized in the liver into less active metabolites and is also excreted primarily through the liver. Therefore, belinostat dosing in patients with hepatic dysfunction should be explored in a clinical trial to establish dosing guidelines.

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients (except those with hepatocellular carcinoma) must have histologically or cytologically confirmed (at original diagnosis or subsequent recurrence or progression) solid tumor or lymphoma that is metastatic, unresectable, progressive, or recurrent, and for which standard curative or palliative measures do not exist or

are no longer effective. Patients with hepatocellular carcinoma do not require biopsy confirmation. A liver mass with raised α-fetoprotein level (≥500 ng/mL), consistent radiographic changes, and serology and viral DNA/RNA measurements consistent with chronic hepatitis[25] (see Section 3.1.9) will be sufficient to identify hepatocellular carcinoma without the need for pathologic confirmation of the diagnosis. Patients with hepatocellular carcinoma must still, however, have disease that has failed standard therapy. Having chronic hepatitis B or C will not exclude patients from participating.

3.1.2 No radiation, major surgery, chemotherapy or biologic therapy within 4 weeks prior to entering the study (6 weeks for nitrosoureas or mitomycin C); ≥ 2 weeks since any prior administration of study drug in an exploratory IND/Phase 0 study (also referred to as an "early Phase I study" or "pre-Phase I study" where a sub-therapeutic dose of drug is administered) at the PI's discretion. Patients must have recovered to at least eligibility levels due to adverse events and/or toxicity of prior chemotherapy or biologic therapy.

3.1.3 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of belinostat in patients < 18 years of age, children are excluded from this study but will be eligible for future pediatric Phase I single-agent trials.

3.1.4 ECOG performance status ≤ 2 (Karnofsky ≥ 60%, see Appendix B).

3.1.5 Life expectancy of greater than 3 months.

3.1.6 Patients must have acceptable renal and marrow function as defined below:

- leukocytes ≥3,000/mcL
- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
- serum creatinine within normal institutional limits

OR

- creatinine clearance ≥60 mL/min for patients with creatinine levels above institutional normal, as determined by a measured 24-hour creatinine clearance

Baseline evaluations should be conducted within 7 days of treatment start date.

3.1.7 Patients with abnormal liver function will be eligible and will be grouped according to the criteria described in Section 5.1. Patients with active hemolysis should be excluded. No distinction will be made between liver dysfunction due to metastases and liver dysfunction due to other causes.

3.1.8 Patients with biliary obstruction for which a stent has been placed are eligible, provided the stent has been in place for at least 10 days prior to the first dose of belinostat and the liver function has stabilized. Two measurements at least 2 days apart that put the patient in the same hepatic dysfunction stratum will be accepted

as evidence of stable hepatic function. There should be no evidence of biliary sepsis.

3.1.9 For patients with hepatocellular carcinoma secondary to hepatitis B or C, test results should be indicative of chronic viral hepatitis infection:

3.1.9.1 Patients with hepatitis B

- Antibodies: HepBsAg and HepBcAb should be elevated and HepBsAb and HepBeAb low, indicating chronic infection. If the pattern is different from this, please notify the PI.
- Viral load: COBAS TaqMan test[26] measuring HBV DNA is reduced in chronic phase hepatitis B. The baseline value as the patient enters this study will be useful to discriminate between drug, disease progression, or increased viral load as possible attributions for worsening symptoms.

3.1.9.2 Patients with hepatitis C

- Antibodies: Anti-HCV testing—specific tests used will be based on the site's standard procedure for identifying hepatitis C.[27-29]
- Viral load: HCV-RNA should be relatively constant in chronic phase of disease, though the level is typically higher than in the acute phase.[27-29] The baseline value as the patient enters this study will be useful to discriminate between drug, disease progression, or increased viral load as possible attributions for worsening symptoms.

3.1.10 Patients with gliomas or brain metastases who require corticosteroids or anticonvulsants must be on a stable dose of corticosteroids and seizure free for 1 month prior to enrollment. Patients with known brain metastases should have had brain irradiation (whole brain or gamma knife) more than 4 weeks before starting the protocol. Note that patients should have had their steroids tapered to low dose (i.e., < 1.5 mg of dexamethasone/day).

3.1.11 The effects of belinostat on the developing human fetus are unknown. For this reason and because HDAC inhibitors 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. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.12 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Prior therapy with belinostat.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 Patients with history of allergic reactions attributed to compounds of similar chemical or biologic composition to belinostat, including hydroxamate compounds or arginine.

3.2.4 Patients should not have taken valproic acid, another HDAC inhibitor, for at least 2 weeks prior to enrollment.

3.2.5 Patients with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Pregnant women are excluded from this study because belinostat is an HDAC inhibitor with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with belinostat, breastfeeding should be discontinued if the mother is treated with belinostat.

3.2.7 Having chronic hepatitis B or C will not exclude patients from participating if they are otherwise eligible; however, requiring treatment with interferon is an exclusion. Patients must be stable without having received interferon in at least 4 weeks.

3.2.8 HIV positive patients *who are not on retroviral therapy* **will not be excluded** from cohort 1, the normal liver function cohort.

HIV positive patients *who are not on retroviral therapy* will be excluded from cohorts 2-4 because of confounding effects from potential complications from HIV and opportunistic infections.

3.2.9 HIV-positive patients *on combination antiretroviral therapy* are ineligible because of the potential for the increased risk of liver dysfunction from the antiretroviral therapies themselves and because of potential PK interactions with belinostat. Appropriate studies will be undertaken in these groups of patients when indicated.

3.2.10 Patients with significant cardiovascular disease (New York Heart Association Class III or IV cardiac disease), symptomatic congestive heart failure, myocardial infarction within the past 6 months, unstable angina, unstable arrhythmia or a need for anti-arrhythmic therapy (use of frequency adjusting medication for atrial fibrillation is allowed, if stable medication for at least last month prior to initiation of belinostat treatment and medication not listed as causing Torsades de Points), or evidence of acute ischemia on ECG. Marked baseline prolongation of QT/QTc interval, e.g., repeated demonstration of a QTc interval > 450 msec; Long QT Syndrome. Concomitant use of drugs known to prolong the QT interval and/or cause Torsades de Pointes (Table 1, Appendix C) is not allowed during the study or within 2 weeks of study entry. These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment. Drugs that may be associated with Torsades de Pointes but lack substantial evidence (Table 2, Appendix C) will be allowed at the discretion of the PI (although it is preferable to substitute an alternate medication), and patients will be closely monitored.

3.3 Inclusion of Women and Minorities

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

3.4 Research Eligibility Evaluation

3.4.1 History and Physical Examination: Complete history and physical examination (including height, weight, vital signs, EKG, and performance score) will be conducted prior to starting study drug administration.

3.4.2 Imaging Studies (Baseline): Every participant should have a clinical evaluation of known sites of disease as part of the baseline evaluation. All patients will be required to undergo a CT scan of the chest/abdomen/pelvis to evaluate sites of disease within 28 days prior to start of study drug administration.

3.4.3 Laboratory Evaluation: Baseline laboratory data are to be obtained within 1 week prior to starting study drug.

3.4.3.1 Hematological Profile: CBC with differential and platelet count.

3.4.3.2 Coagulation Studies: PT*/INR/aPTT* is required to be checked at baseline
*=as clinically indicated

3.4.3.3 Biochemical Profile: electrolytes, BUN, creatinine, glucose, AST, ALT, bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase.

3.4.3.4 Serum pregnancy test for female participants of childbearing age and anatomic ability.

3.4.4 Histologic confirmation will be required prior to enrollment (except for patients with hepatocellular carcinoma; see Section 3.1.1). A pathology report from the time of diagnosis will be required from each participant to confirm diagnosis. A pathology report from a known recurrence will be accepted if the original report is not available.

3.4.5 Laboratory evaluation for patients with hepatocellular carcinoma secondary to hepatitis B or C:

3.4.5.1 For patients with hepatitis B:

- HepBsAg, HepBcAb, HepBsAb, and HepBeAb; results may be from within 3 months before starting on study.
- COBAS TaqMan; results must be from within 1 month before starting on study.

3.4.5.2 For patients with hepatitis C:

- anti-HCV; results may be from within 3 months before starting on study.
- HCV-RNA; results must be from within 1 month before starting on study.

3.4.6 Child-Pugh Classification (CPC) of liver dysfunction: each patient's CPC score should be calculated during the eligibility assessment and submitted with the protocol registration at enrollment. See Appendix M for instructions on CPC calculation.

4 REGISTRATION PROCEDURES

4.1 Registration Process

Registrations for the trial must be made through the Coordinating Center at the National Cancer Institute. Patients are registered Monday through Friday between the hours or 8:30am through 4:30pm, excluding Federal Holidays. Prior to patient registration, documentation of IRB approval by collaborating institutions must be on file.

Slot Reservation
Once a patient has been identified for potential enrollment, the participating site's data manager or research nurse must contact the Developmental Therapeutics Clinic (DTC) Research Nurse at (301) 435-4949. (See Appendix H for slot reservation procedures).

4.1.1 Coordinating Site Registration Process

Authorized staff must register an eligible candidate with the NCI Central Registration Office (CRO). A registration Eligibility Checklist from the Web site (http:// home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) (ncicentralregistration-l@mail.nih.gov). After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents. Verification of Registration will be forwarded electronically via e-mail.

4.1.2 Participating Site Registration (Appendix H)

Registration will be done centrally by the Coordinating Center at the NCI per the detailed instructions in Appendix H. A protocol registration form and a cover memo will be supplied by the Coordinating Center, NCI DTC (See Appendix J for Eligibility/Pre-Registration Worksheet) and updates will be provided as needed. Patient eligibility and demographic information is required for registration. To register a patient, fax copies of the following pre-registration documents, signed informed consent, HIPAA authorization form, required pre-study tests (baseline laboratory and pathology reports), and the completed Eligibility/Pre-Registration form to the Coordinating Center's Research Nurse Nancy Moore, RN, phone (240) 760-6045 (nancy.moore@nih.gov). The Coordinating Center will notify the participating site by e-mail to confirm that the protocol registration documents have been received.

All eligible patients will be registered though the NCI Center Registration Office (CRO). The CRO is open from 8:30 am to 5:00 pm EST Monday through Friday, excluding federal holidays. The Coordinating Center's research nurse will complete and fax a registration Eligibility Checklist from the web site (http:// home.ccr.cancer.gov/intra/eligibility/welcome.htm). After confirmation of eligibility at the Central Registration Office, CRO staff will assign a unique patient/subject ID number for each patient that will be used to enter data into the C3D database. An encrypted electronic verification of registration form will be sent to the NCI research nurse. The Coordinating Center's research nurse will assign a dose, and a patient study ID number. This information will be included on the confirmation of registration form. The confirmation form will be sent to the data manager or research nurse by email. The assigned patient ID will be used to code research samples and reference patients during the Organ Dysfunction Working Group conference call (See Appendices H and I for Registration Procedures and Conference Call Procedures). Questions about eligibility should be directed to the Coordinating Center's Research Nurse.

Following registration, patients should begin protocol treatment within 72 hours. Issues that would cause treatment delays should be discussed with the Principal Investigator. If a patient does not receive protocol therapy following registration, the patient's registration on the study may be canceled. The Study Coordinator should be notified of cancellations as soon as possible.

4.1.3 Off-Study Procedure

Off-Study Procedure: Authorized staff must notify the Coordinating Center's Research Nurse when a patient is taken off study. The off study form is included in Appendix K and must be completed and sent via encrypted email to: NCI Central Registration Office (HOIS) (ncicentralregistration-l@mail.nih.gov).

5 TREATMENT PLAN

5.1 Belinostat Administration

Treatment will be administered on an outpatient basis. On days when belinostat is given, it will be administered IV over 30 minutes. Either peripheral or central IV can be used. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for belinostat are described in Section 6. No investigational or commercial agents or therapies for the purpose of treating the malignancy may be administered while the patient receives belinostat.

5.1.1 Stratification by Hepatic Dysfunction Group

Patients will be divided into 4 cohorts based on their level of liver dysfunction:

Cohort 1: Normal hepatic function: bilirubin ≤ ULN **and** AST ≤ ULN

Cohort 2: Mild hepatic dysfunction: bilirubin > ULN but ≤ 1.5 x ULN **and/or** AST > ULN

Cohort 3: Moderate hepatic dysfunction: bilirubin > 1.5 x ULN to ≤ 3 x ULN and any AST

Cohort 4: Severe hepatic dysfunction: bilirubin > 3 x ULN but ≤ 10 x ULN and any AST

5.1.2 Schedule

On Day -7 (Cycle 1 only), patients in all cohorts will receive belinostat 400 mg/m^2 and have baseline and post-dose blood samples collected for PK measurements (Section 9.1; post-dose samples collected 15 and 25 minutes after starting infusion, and then at the following time points after the end of infusion: 5, 10, 15, 30, 60, 90 minutes, 2, 4, 6, 8, and 24 hours).

On Days 1–5 of each cycle, patients in all cohorts will receive their assigned dose of belinostat based on their level of hepatic toxicity, according to the table below. Dose escalation will begin at dose level 1.

Including Day -7, the total duration of Cycle 1 will be 28 days. All other cycles will be 21 days.

A new cycle may begin 1 day earlier or 1 day later than it would otherwise be scheduled based on the 28 days for cycle 1 and the 21 days for the other cycles, i.e., the second cycle may begin on day 27, 28, or 29 and the third and later cycles may begin on day 20, 21, or 22, to allow for flexibility for days the clinic is closed and other unexpected events.

Although belinostat's effect on cardiovascular safety parameters is not assessed as a major concern, for patient safety, an EKG will be done after 5 days of belinostat at the cohort-

assigned dose (Cycle 1 Day 5) and again pre-Cycle 2 to evaluate for any elevation in QTc after cumulative exposure.

5.1.3 Dose Escalation Scheme

	Dose Level of Belinostat (mg/m^2/day)				
	-1	**1**	**2**	**3**	**4**
Cohorts: Normal	750	1000	No escalation	No escalation	No escalation
Mild Dysfunction	500	750	1000	No escalation	No escalation
Moderate Dysfunction	250	500	750	1000	No escalation
Severe Dysfunction	125	250	350	500	750

Each patient's starting dose will be assigned by the Coordinating Center at the time of registration according to the dose escalation scheme and hepatic dysfunction criteria outlined above. Patients whose degree of hepatic dysfunction changes (becomes worse or better) between registration and initiation of protocol therapy may be re-assigned to a different dysfunction group and dose level. This change should be discussed with the Principal Investigator. The Coordinating Center must document reassignments with notification to Theradex.

All cohorts can accrue simultaneously. Doses in more severe cohorts will not be escalated beyond doses being tested in less severe cohorts. If DLT-level toxicity is noted in dose level 1, then dose de-escalation to level -1 may occur. A patient will be dose reduced to the next lowest dose level if they experience and recover from a Grade 4 adverse event (see Section 6.1.1.).

5.1.4 Definition of Evaluable and Complete Cycle

A cycle is defined as 21 days, with Day 1 starting the first day of the 5-day treatment period. If a patient receives the total dose of belinostat as planned over the course of 5 days and remains in the study until Day 21, unless taken off treatment for toxicity, the patient will be considered to have completed a cycle of therapy and will be considered evaluable. Patients who do not complete a cycle of therapy for reasons other than toxicity will be replaced. Patients who experience a DLT on day -7 will be taken off treatment. They will not be treated with the 5-day course. This will be considered a DLT for study purposes and will affect dose escalation for that cohort.

5.1.5 Maintaining Consistent Dosing Across the Hepatic Dysfunction Groups

In general, results from each hepatic dysfunction group will have implications for the other groups based upon the assumption that at any given dose level, the dysfunction-

toxicity response gradient is monotonic. In other words, patients in a particular group will not tolerate a dose not tolerated by a group with lesser dysfunction and conversely, will tolerate a dose tolerated by a group with greater dysfunction. When discrepancies arise between observed results and this principle, they will be resolved in the direction of conservative practice. That is, the lower dose will be recommended for both groups if a higher dose is tolerated in a group of greater dysfunction, but not in the group of lesser dysfunction. In particular, dose level assignments and MTD determination will be made consistent across the various hepatic dysfunction groups as follows:

Observation for a Particular Dysfunction Group	**Resulting Action for other Dysfunction Groups**
MTD has been exceeded at a dose level.	Accrual at that dose level or higher is terminated for all cohorts with greater hepatic dysfunction.
MTD has been established at a dose level.	Accrual at lower dose levels is terminated for all cohorts with lesser hepatic dysfunction. New patients will be enrolled at the dose found to be safe in the higher hepatic dysfunction cohort.*
MTD has been established in one cohort while simultaneously the MTD has been exceeded at that dose in a cohort with lesser dysfunction.	The MTD in both cohorts is determined to be the dose of the cohort with the lesser hepatic dysfunction.

* For example, if a dose of 1000 mg/m^2 is found to be safe for the moderate dysfunction cohort, then enrollment will be terminated to the 750 mg/m^2 cohorts of the mild dysfunction cohort and all subsequent patients will be enrolled at the 1000 mg/m^2 cohort. No changes will be made to the enrollment for the severe dysfunction cohort.

5.2 Definition of Dose-Limiting Toxicity

DLT will be a toxicity that occurs during Cycle 1 and is felt to be possibly, probably, or definitely related to the study drug and meets the following criteria:

5.2.1 Grade ≥3 non-hematologic toxicity will be considered dose-limiting, with the following exceptions:

- Allergic reaction/hypersensitivity will not be considered dose limiting.
- Alopecia will not be considered dose limiting.
- Grade ≥3 diarrhea will only be considered dose limiting if, after 24 hours, it is refractory to treatment.
- Grade ≥3 nausea and vomiting will only be considered dose limiting if after 24 hours it is refractory to maximal anti-emetic therapy and unable to be corrected to Grade 1 or baseline.
- Grade 3 rise in creatinine, not corrected to Grade 1 or baseline after fluids within 24 hours, will be considered dose limiting. All Grade 4 rises in creatinine will be dose limiting.
- Grade ≥3 electrolyte toxicities unable to be corrected to Grade 1 or baseline within 48 hours will be considered dose limiting.

- Elevated bilirubin will be defined as DLT by the criteria as specified in Section 5.2.4.

5.2.2 Grade 4 hematological toxicity

- Neutropenia: Drug-related Grade 4 neutropenia for >5 days without fever or infection will be considered dose limiting. Grade 4 neutropenia of any duration accompanied by fever or infection will be considered dose limiting.
- Grade 4 thrombocytopenia.
- Grade 4 lymphopenia, anemia, or leucopenia without neutropenia will NOT constitute a DLT.

5.2.3 Any neurotoxicity Grade ≥ 2 that is not reversible to a Grade ≤ 1 or baseline within 2 weeks will be considered dose limiting. For patients with neuropathy at baseline, an increase in grade that does not reverse within 2 weeks and is felt to be drug related will be considered a DLT.

5.2.4 Liver toxicity as described:

Worsening liver function, as defined by a rise in serum bilirubin, not related to tumor progression, stent occlusion, or worsening viral hepatitis will constitute a DLT if a patient in the mild group progresses into the severe dysfunction range for 1 week, or if a patient in either the moderate or severe groups has a > 1.5 times increase in bilirubin lasting 1 week. (Note: In the moderate cohort, a > 1.5 times increase over baseline level of total bilirubin that does not put a patient in the severe group does not constitute a DLT).

5.2.5 Delays in new treatment cycles by ≥ 2 weeks due to treatment-related toxicity will constitute a DLT.

Management and dose modifications associated with the above AEs are outlined in Section 6.

5.3 Design

Twelve patients will be enrolled on the normal hepatic function cohort (cohort 1). Cohort 2 will undergo dose escalation according to a 3+3 design. The remaining cohorts (cohort 3 and 4) will undergo a similar dose escalation design to cohort 2, but with the flexibility to over accrue an additional 1 or 2 patients per dose level. See Section 6 for intrapatient dose modification guidelines.

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 at least 3 more patients at this dose level. • If 0 of these 3 patients experience DLT, proceed to the next dose level. • If 1 or more of this group suffer DLT, then dose escalation is stopped, and this dose is declared the maximally administered dose. 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 6 at highest dose level below the maximally administered dose	This is generally the recommended phase 2 dose. At least 6 patients must be entered at the recommended phase 2 dose.

5.4 Supportive Care Guidelines

Patients should be provided supportive care as medically indicated. This includes blood product support, antibiotic treatment, and management of any other medical conditions.

Prophylactic measures for nausea/vomiting are allowed.

If diarrhea develops and does not have an identifiable cause other than study drug administration, anti-diarrheals such as Lomotil (diphenoxylate HCl 2.5 mg + atropine sulfate 0.025 mg/tablet) dosed according to package insert or loperamide 4 mg po after the first unformed stool with 2 mg po every 2 hours as long as unformed stools continue (4 mg every 4 hours while asleep). No more than 16 mg of loperamide should be taken in during a 24-hour period. This regimen can be repeated for each diarrheal episode. Diarrhea will be considered refractory if it does not resolve within 24 hours = to Grade 2 with the above regimen (16 mg, or less if there is resolution of the symptoms, of loperamide in a 24-hour period).

5.5 General Concomitant Medication

All concurrent medications should be documented prior to initiation of treatment, and be periodically reviewed with the patient. Particular attention must be paid to medications which may prolong the QTc interval (Appendix C) and agents that interact with CYP450 isoenzymes (Appendix D).

QTc Prolongation:
Caution should be exercised when administering belinostat to patients with a history of QTc interval prolongation, in patients taking anti-arrhythmics or other medications that may prolong the QTc interval, and those with relevant pre-existing cardiac disease. As Appendix C/Table 1 includes medications that are generally accepted to carry the risk of causing QTc prolongation and Torsades de Pointes, patients requiring those medications will not be eligible for this protocol.

Use of these drugs is not allowed within 2 weeks of study entry, while the patient is on protocol, and within 4 weeks of ending protocol treatment. Those medications listed in Appendix C/Table2 as reported but lacking substantial evidence for causing QTc prolongation and Torsades de Pointes will be allowed at the discretion of the PI, although if an alternative medication can be substituted, that would be preferable. If the patient remains on a medication in Table 2, they should have an EKG prior to each cycle.

CYP450 Interactions:
At the present time, no in vivo human studies have been conducted to elucidate the metabolic and drug interaction profiles of belinostat. *In vitro* data indicate that belinostat is an inhibitor of CYP2C8 and CYP2C9. Belinostat is a potential inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and CYP3A4. There is evidence that belinostat is a substrate of CYP2D6 and CYP3A4. Attention and caution must be used when patients are on belinostat and another medication that might affect any of these isoenzymes (Appendix D).

5.6 Duration of Therapy

In the absence of treatment delays due to adverse events, 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.

5.7 Duration of Follow Up

Patients will be followed for 30 days after the last dose is administered or until one of the following occurs: patient enrolls on another protocol (phase 0 or early phase I), patient receives standard of care, or death, whichever comes first. The follow-up will consist of a phone call between Days 27-30 after the last dose to evaluate adverse events that were ongoing and any new events that might be deemed related to the therapy. Unacceptable toxicities (i.e., AEs related to the intervention) that have not resolved by Day 30 post-treatment will be followed via biweekly phone calls until stabilization or resolution.

5.8 Criteria for Removal From Study

Patients will be removed from study for one of the following reasons:

- patient completed 30-day follow-up period,
- patient experiences an infusion or allergic reaction to belinostat which consists of bronchospasm, shortness of breath, hypoxia, or hypotension,
- toxicities are unresolved but stabilized,

- patient enrolls on another protocol (phase 0 or early phase I), or
- patient receives standard of care.

The reason for study removal and the date the patient was removed must be documented in the medical record.

6 DOSING DELAYS/DOSE MODIFICATIONS

6.1 Intrapatient Dosing, Non-Hepatic Toxicities

There will be no dose modification for lymphopenia, anemia, or leucopenia without neutropenia of any grade.

6.1.1 Patients who experience a non-hepatic toxicity > Grade 1 but < Grade 4 may proceed to a subsequent cycle at the same dose level if the toxicity improves to Grade 1 or to baseline within 2 weeks of the previous cycle. Patients who experience a Grade 4 dose limiting toxicity may proceed to a subsequent cycle at the next lower dose level if their toxicity improves to Grade 1 or to baseline within 2 weeks of the previous cycle. If any toxicity > Grade 1 does not improve to Grade 1 or baseline within 2 weeks, the patient will come off treatment.

6.1.2 In the case of a single occurrence of grade 4 QTc prolongation (QTc > 500 msec in combination with life-threatening signs or symptoms, e.g., arrhythmia, CHF, hypotension, shock, syncope; Torsades de pointes), belinostat should be discontinued permanently.

6.1.3 In the event of a Grade 3 QTc prolongation (QTc >500 msec; without life-threatening symptoms described above), study treatment should be temporarily withheld until the QTc interval returns below 500 msec. Patients should be monitored with daily ECGs until the QTc interval returns below 500 msec. Treatment may then be resumed at the next lower dose level.

In the event of a subsequent prolongation of QTc interval >500 msec after 2 dose reductions according to above, further treatment with belinostat should be discontinued.

6.1.4 In the event of an infusion reaction or allergic reaction to belinostat, the patient will be treated with antihistamines, steroids, and/or epinephrine, as appropriate.

a. Patients who experience an infusion or allergic reaction to belinostat consisting of rash, itchy throat, or mild cough can remain on study and be premedicated for all future doses. If a similar or worse reaction occurs when the patient

receives belinostat after being premedicated, the patient will not be re-exposed, and will come off study.

b. Patients who experience an infusion or allergic reaction to belinostat consisting of bronchospasm, shortness of breath, hypoxia, or hypotension will not be re-exposed, and the patient will come off study.

6.2 Intrapatient Dosing, Hepatic Toxicities

6.2.1 Treatment for an individual patient will stop immediately when the bilirubin rises to the level of a DLT. Treatment for that patient can resume after a DLT under the following conditions:

- The bilirubin of a patient in the mild cohort returns to at least the moderate dysfunction range within 2 weeks. The patient will be treated at one dose level lower (unless they are already on dose level -1, in which case they will be taken off treatment) or at the dose for moderate dysfunction, whichever is lower.
- The bilirubin of a patient in the moderate cohort returns to the range of moderate dysfunction within 2 weeks. The patient will be treated at one dose level lower unless they are already on dose level -1, in which case they will be taken off treatment.
- The bilirubin of a patient in the severe cohort returns to ≤ 1.2 x baseline bilirubin within 2 weeks. The patient will be treated at one dose level lower unless they are already on dose level -1, in which case they will be taken off treatment.

If the bilirubin does not return to within the above-stated ranges within 2 weeks, the patient will be taken off treatment.

6.2.2 If a patient has worsening liver function that leads to a cohort change but does not constitute a DLT, they will be treated according to the dose level being used for their new cohort, except if that dose is the same or higher than the dose on which they have already been treated. If the dose of their new cohort is the same or higher, they will be treated at one dose level lower than the previous dose that they received.

6.2.3 If a patient experiences an improvement in liver function during treatment, there will be no change in dose during an ongoing cycle, but treatment may resume at a new dose level determined by the cohort that would apply based on their liver function, if there is continued improvement at the time of the next cycle.

7 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event monitoring and reporting is a routine part of every clinical trial. The following list of adverse events (Section 7.1) and the characteristics of an observed adverse event (Section 7.2) will determine whether the event requires **expedited** (via CTEP-AERS; Section 7.3) or **routine** (via CTMS; Section 7.4) reporting.

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Belinostat (PXD 101, NSC 726630)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 583 patients*. Below is the CAEPR for belinostat (PXD 101).

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.6, September 12, 2016[1]

Adverse Events with Possible Relationship to Belinostat (PXD-101) (CTCAE 4.0 Term) [n= 583]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Edema limbs		***Edema limbs (Gr 2)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		
INFECTIONS AND INFESTATIONS			

Adverse Events with Possible Relationship to Belinostat (PXD-101) (CTCAE 4.0 Term) [n= 583]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Infection[2]		***Infection[2] (Gr 3)***
INVESTIGATIONS			
	Creatinine increased		
	Electrocardiogram QT corrected interval prolonged		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
	Dehydration		
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Dysgeusia		
	Headache		***Headache (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Dyspnea		***Dyspnea (Gr 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		
VASCULAR DISORDERS			
	Flushing		***Flushing (Gr 2)***

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

[2]Infection may include any of the 75 infection sites under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on belinostat (PXD-101) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that belinostat (PXD-101) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Cardiac disorders - Other (bundle branch block left); Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular fibrillation
EYE DISORDERS - Eye disorders - Other (visual acuity reduced); Eye disorders - Other (visual loss)
GASTROINTESTINAL DISORDERS - Abdominal distension; Dyspepsia; Gastroesophageal reflux disease; Mucositis oral; Rectal hemorrhage; Small intestinal obstruction; Upper gastrointestinal hemorrhage
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Flu like symptoms; General disorders and administration site conditions - Other (general physical health deterioration); Infusion related reaction; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatic cirrhosis)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Tracheal hemorrhage
INVESTIGATIONS - Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Cardiac troponin I increased; Cholesterol

high; Ejection fraction decreased; INR increased; Investigations - Other (electrocardiogram T wave inversion); Investigations - Other (prothrombin time shortened); Investigations - Other (total protein decrease); Lipase increased; Weight gain; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hypermagnesemia; Hypertriglyceridemia; Hypoalbuminemia; Hypocalcemia; Hypokalemia; Hyponatremia; Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthralgia; Back pain; Bone pain; Chest wall pain; Generalized muscle weakness; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Depressed level of consciousness; Dysesthesia; Encephalopathy; Lethargy; Nervous system disorders - Other (apraxia); Nervous system disorders - Other (burning sensation); Peripheral sensory neuropathy; Seizure; Stroke; Syncope
PSYCHIATRIC DISORDERS - Confusion; Depression; Insomnia; Psychosis
RENAL AND URINARY DISORDERS - Acute kidney injury; Renal and urinary disorders - Other (azotemia); Urinary frequency
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Genital edema; Vaginal inflammation
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Cough; Hiccups; Hypoxia; Nasal congestion; Pneumonitis; Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Hyperhidrosis; Pruritus; Urticaria
VASCULAR DISORDERS - Hematoma; Hypertension; Hypotension; Phlebitis; Thromboembolic event; Vasculitis

Note: Belinostat (PXD-101) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.2 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

'Expectedness': AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Section 7.1).

Attribution of the AE:

- Definite – The adverse event *is clearly related* to the study treatment.
- Probable – The adverse event *is likely related* to the study treatment.
- Possible – The adverse event *may be related* to the study treatment.
- Unlikely – The adverse event *is doubtfully related* to the study treatment.
- Unrelated – The adverse event *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Expedited adverse event reporting for this study is via CTEP-AERS (CTEP Adverse Event Expedited Reporting System), accessed via the CTEP homepage (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "NCI Guidelines: Expedited Adverse Event Reporting Requirements for NCI Investigational Agents" which can be downloaded from the CTEP web site (http://ctep.cancer.gov).

In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497, or 301-897-7402 for CIP studies. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: Study Coordinator of the Lead Organization, Principal Investigator, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.3.2 Expedited Reporting Guidelines – CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 1 Trials

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study must be reported using expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of designation as expected or unexpected and attribution with the exception of events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

7.3.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

- For this protocol only, certain adverse events/grades are exceptions to the Expedited Reporting guidelines and do not require expedited reporting. The following adverse events should be reported through the routine reporting mechanism (Section 7.4):

  any grade lymphopenia, Grade 2 electrolyte abnormalities, alopecia (any grade), anemia (grade 2), albumin (grade 2), hyperuricemia (grade 3), INR (grade 2), and PTT (grade 2) will NOT be reported through CTEP-AERS but will be reported in the routine data submissions.

- Events that are clearly consequences of the "main" event (e.g., hypokalemia associated with diarrhea or the arrhythmias, hypotension, hypoxia, etc. that are known to occur concurrently with sepsis) may be noted in the Description of Event in the CTEP-AERS report and do not require separate CTEP-AERS reports.

- The possibility of the contribution of comorbid conditions to the event should be considered when reporting adverse events. Examples include hyperglycemia in patients with diabetes, or headaches and seizures in patients with brain tumors.

7.3.4 Pregnancy, Fetal Death and Death Neonatal

NOTE: When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or
"Neonatal loss", the Pregnancy Information Form should also be completed for patients who became pregnant on study, and faxed along with any additional medical information to **301-230-0159.** The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in

the "Description of Event" section of the CTEP-AERS report.

7.3.4.1 Pregnancy

- Because patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic, DCTD/DCP is requesting that pregnancy should be reported in an expedited manner via CTEP-AERS as Grade 3 "*Pregnancy, puerperium and perinatal conditions - Other (pregnancy)*" under the *Pregnancy, puerperium and perinatal conditions* SOC.

- The pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

7.3.4.2 Fetal Death

- Fetal death is defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation."
- Any fetal death should be reported expeditiously, as Grade 4 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy loss)" under the Pregnancy, puerperium and perinatal conditions SOC.
- A fetal death should NOT be reported as "Fetal death," a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.

7.3.4.3 Death Neonatal

- Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.
- A neonatal death should be reported expeditiously as Grade 4 "General disorders and administration - Other (neonatal loss)" under the General disorders and administration SOC.
- Neonatal death should NOT be reported as "Death neonatal" under the General disorders and administration SOC, a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.

7.3.5 NCI-IRB Expedited Reporting of Adverse Events, Unanticipated Problems, and Deaths

7.3.5.1 Definitions

Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until satisfactory resolution. AEs should be reported up to 30 days following the last dose of study drug. AEs that are considered treatment related, expected, continuing, but not resolvable by 30 days after treatment completion (e.g., alopecia) will not be followed after the 30-day period.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact
- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

Suspected adverse reaction

Suspected adverse reaction means 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. A 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 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. "Unexpected", 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.

Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare, or rights of subjects or others.

Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience 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.

Disability

A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

Protocol Deviation (NIH Definition)
Any change, divergence, or departure from the IRB approved study procedures in a research protocol

Non-compliance (NIH Definition)
The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

Unanticipated Problem
Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and
  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a g*reater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.5.2 **NCI-IRB and Clinical Director Reporting**

NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths
*The NCI-IRB **requires** that the following language be used for reporting events to the NCI-IRB and the Clinical Director:*

The Coordinating Center PI will report to the NCI-IRB:

- All unexpected serious adverse events that are possibly, probably, or definitely related to the research
- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of Coordinating Center PI awareness via iRIS.

7.3.5.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of unanticipated problem will need to be reported to the NCI IRB.

7.3.6 Multicenter Guidelines for Expedited Adverse Event Reporting

7.3.6.1 Expedited Adverse Event Reporting for Participating Sites

Adverse Event Reporting via CTEP-AERS:
Participating sites are responsible for submitting any expedited adverse event reports directly to CTEP. Follow sponsor expedited AE reporting requirements in Section 7.3.2. Copy Nancy Moore (nancy.moore@nih.gov) and Naoko Takebe, MD (takeben@mail.nih.gov) on all CTEP-AERS reports.

Adverse Event Reporting to NCI IRB:
The site PI must immediately report to the Coordinating Center PI any serious adverse event, whether or not considered drug related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the drug caused the event within 24 hours of PI awareness of the event. The site PI must also report any protocol deviations or violations to the Coordinating Center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

7.4 Routine Adverse Event Reporting

Those adverse events that do not require expedited reporting **must** be reported in routine study data submissions via CTMS (see Section 12.1). **Adverse events reported through CTEP-AERS must also be reported in routine study data submissions.**

7.4.1 NCI-IRB Requirements for PI Reporting of Adverse Events at Continuing Review:

Please use the following table for reporting adverse events at time of CR:

System Organ Class	CTCAE Term	Grade	# of Events since last CR	Total # of Events	Attribution to Research	Serious?	Unexpected?

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.

2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.5 Secondary AML/MDS

AML/MDS events are to be reported via CTEP-AERS (in addition to your routine AE reporting mechanisms). In CTCAE v4.0, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.

8 PHARMACEUTICAL INFORMATION

Chemical Name: N-hydroxy-3-[3-(phenylsulfamoyl)phenyl]prop-2-enamide

Other Names: PXD101

Classification: Histone deacetylase (HDAC) inhibitor

CAS Registry Number: 414864-00-9

Molecular Formula: $C_{15}H_{14}N_2O_4S$ **M.W.:** 318.35

Approximate Solubility: Water 0.14 mg/mL; ethanol >200 mg/mL; polyethylene glycol 400 ~ 1.5 mg/mL; 1,2-propanediol ~ 0.2 mg/mL

Mode of Action: Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones. Belinostat is a novel and potent HDAC inhibitor of the hydroxymate class. It alters acetylation levels of histone and non-histone proteins, thus influencing chromatin accessibility and ultimately gene transcription. Additionally, recent data reveals that HDAC inhibitors reduce vascular endothelial growth factor (VEGF) production and directly inhibit the endothelial cells proliferation.

Description: A yellow solid powder

How Supplied: TopoTarget A/S supplies and the CTEP, DCTD, NCI distributes belinostat in single-use 30 mL clear glass vials with coated stoppers and aluminum crimp seals with "flip-off" caps containing 500 mg belinostat For Injection. The lyophilized product also contains arginine, Ph. Eur/USP.

Preparation: Reconstitute the lyophilized product with 9 mL Sterile Water for Injection to yield a concentration of belinostat of 50 mg/mL. Before intravenous administration, further dilute in 250 mL 0.9 % Sodium Chloride Injection.

Storage: Store intact vials of belinostat at ambient room temperature (15-25°C; 59- 77°F); brief excursions permitted (15-30°C; 59-86 °F). Leave intact vials of belinostat in the secondary packaging until use.

Stability: Shelf life stability studies of intact vials of belinostat are on-going; once the lyophilized product is reconstituted, use it immediately.

Once further diluted in 250 mL of 0.9% sodium chloride, belinostat may be stored at ambient room temperature (15-25°C) for up to 24 hours, including the infusion time.

Route of Administration: Intravenous

Method of Administration: Infuse belinostat intravenously over 30 minutes through an in-line 0.22 micron low protein binding filter.

Drug Interactions: Belinostat and its metabolites are a weak to moderate inhibitor of CYP2C8 and a moderate to strong inhibitor of CYP2C9. Additionally, CYP3A4 contributes to belinostat metabolism. Avoid moderate to strong CYP3A4 inhibitors or inducers and CYP2C8 and CYP2C9 substrates during belinostat treatment unless deemed medically necessary. As glucuronidation is the major route of elimination for belinostat, caution should be exercised when using concomitant medications that are inhibitors of the UGT1A1 enzyme.

Patient Care Implications: Patients must not use concomitant medication on belinostat infusion days that may cause Torsade de Pointes.

Availability

Belinostat is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI. Belinostat is provided to the NCI under a Clinical Trials Agreement (CTA) between TopoTarget and the DCTD, NCI (see Section 12.3).

Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of investigational agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or e-mail PMBAfterHours@mail.nih.gov anytime.

Agent Accountability

Agent Inventory Records – The Investigator, or a responsible party designated by the Investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)
Investigator Brochure Availability – The current versions of the IBs for PMB-supplied agents will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment

of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status and a "current" password. Questions about IB access may be directed to the PMB IB coordinator at IBCoordinator@mail.nih.gov.

9 CORRELATIVE/SPECIAL STUDIES

Pharmacokinetic studies will be done on all patients at all participating sites. This can be waived at the Principal Investigator's discretion for patient hardship, including lack of venous access. In this event, patients will be replaced to ensure that adequate PK data are obtained for each group (i.e., at least 3 patients per group and at least 6 patients at the MTD level).

9.1 Pharmacokinetic Studies

All PK measurements for this study will be performed and analyzed by the Clinical Pharmacology Analytical Facility at the University of Pittsburgh Cancer Institute. All data and results will be made available to the investigators on this study, to the industrial collaborator, and to CTEP. PK sampling will be performed on day -7 of the first cycle for all patients.

9.1.1 Specimen Collection / Documentation

Prior to drug administration on day -7 of treatment, an indwelling heparin lock should be placed so that serial specimens can be collected. At each sampling time, 1 mL of blood will be withdrawn and discarded to assure that the solution used to maintain catheter patency does not dilute the sample. Even if a patient has a central venous catheter, it is preferable for day -7 PK samples to be withdrawn through a peripheral heparin lock. However, if the patient objects or has problems with peripheral venous access, the central venous catheter may be used for PK sampling. In the event that the central venous catheter is used, sufficient blood should be withdrawn before each PK sample to assure that the solution used to maintain catheter patency does not dilute the PK sample. It is important to document whether the sample was collected through a heparin lock or central venous catheter.

9.1.2 Pharmacokinetic Sampling Schedule

On day -7 of cycle 1, belinostat will be administered at a dose of 400 mg/m^2 to all patients, under supervision in the outpatient/inpatient research center. The time of belinostat administration should be documented. Blood samples will be drawn at the following time-points for PK studies:

1. Before administration of belinostat
2. 15 minutes after start of infusion of belinostat
3. 25 minutes after start of infusion of belinostat
4. 5 minutes after end of infusion of belinostat
5. 10 minutes after end of infusion of belinostat
6. 15 minutes after end of infusion of belinostat
7. 30 minutes after end of infusion of belinostat

8. 60 minutes after end of infusion of belinostat
9. 90 minutes after end of infusion of belinostat
10. 2 hours after end of infusion of belinostat
11. 4 hours after end of infusion of belinostat
12. 6 hours after end of infusion of belinostat
13. 8 hours after end of infusion of belinostat*
14. 24 hours after end of infusion of belinostat

*It may not always be feasible to obtain the 8 h sample for logistical reasons.

9.1.3 Blood Sample Processing Procedures

1. 4 mL of blood will be collected in a green-top vacutainer tube (heparin anticoagulated) (BD Franklin Lakes, NJ) at the above-mentioned time-points.
2. Centrifuge the sample at 1,000 X g for 10 minutes at 4°C.
3. The resulting plasma samples will be transferred to 3.6 mL NUNC internal thread round bottom cryotubes (NUNC 366524) with labels attached.
4. Samples will be immediately stored at –70 °C until transfer to central PK lab on DRY ICE.

Care must be taken to ensure that labels are carefully attached to tubes and are not likely to fall off when frozen or during shipping. Sample acquisition should be documented on the appropriate sample acquisition form that documents the patient identifier, date, the time that belinostat was administered, the theoretical time of correct sample acquisition, the actual time of sample acquisition, and any problems with sample acquisition (Appendix F: Sample Acquisition Form).

Samples should be stored at –70ºC until shipment to the University of Pittsburgh Cancer Institute. Samples should be shipped to the following name and address:

Clinical Pharmacology Analytical Facility
Attention: Dr. Jan H. Beumer
University of Pittsburgh Cancer Institute
Room G28, Hillman Research Pavilion
5117 Centre Avenue
Pittsburgh, PA 15213-1863

Samples should be shipped on dry ice without thawing. Samples should be wrapped in paper toweling or absorbent underpadding (benchkote); at no point should they come into direct contact with dry ice, which might lead to cracking of the tubes. Samples should be accompanied by the appropriate sample acquisition and shipping form that indicates the material indicated in the above section of the protocol and also indicates the condition of the sample upon shipment, the name of the individual shipping the samples and a phone number, fax number and e-mail contact for confirmation of sample receipt in Pittsburgh.

Samples should be shipped to Pittsburgh by overnight express mail and should only be shipped on Monday, Tuesday, or Wednesday to ensure that samples do not arrive on Saturday or Sunday. Before shipping samples, please notify the Clinical Pharmacology Analytical Facility by calling (412) 623-1213 or (412) 623-3248 or by faxing Dr. Beumer at (412) 623-1212.

9.2 Analysis of Pharmacokinetic Data

Concentrations of belinostat and metabolites will be quantitated with a liquid chromatography-electrospray ionization tandem mass spectrometric method developed and validated in the Clinical Pharmacology Analytical Facility. Plasma concentration versus time data for belinostat and metabolites will be analyzed non-compartmentally using PK solutions and/or compartmentally using ADAPT5. Pharmacokinetic parameters such as Cmax, Tmax, AUC, Cl, Vd and t½ will be calculated and reported.

9.3 Sample Handling

Biospecimens will be collected and processed using validated SOPs that will ensure both specimen quality and patient confidentiality pursuant to informed consent provisions.

Using a computerized inventory system and a backup hardcopy process, all specimen collection and processing steps will be documented and the specific location of each specimen will be tracked. Each new specimen collected will be assigned a unique barcode identifier that can be linked to the original specimen collected and other relevant information within the inventory system. To ensure patient confidentiality, only containers used for the initial specimen collections will be labeled with patient identifiers.

Only the barcode identifier will be applied to all subsequent specimen containers. When specimens are processed and aliquoted, no patient information will be included on the new containers. Original specimen containers will be discarded. Only barcode-labeled specimens without patient identifiers will be shipped for analysis and/or storage. Specimen labels will indicate: protocol number, order in which the patient enrolled on the trial, type of sample, collection time, and total volume collected, as appropriate. Samples from sets of at least three patients will be grouped for scientific analysis.

The inventory process contains other security provisions sufficient to safeguard patient privacy and confidentiality. Access to the inventory system and associated documents will be restricted to appropriate individuals. Requests to use specimens stored in the repository must be approved. The only patient information available in the inventory system will be the patient sex, diagnosis, and level of informed consent given. SOPs ensure that any changes in informed consent made by a patient and relayed to the PI will be reflected in the inventory system to ensure that specimens are destroyed as appropriate. All laboratory personnel will be trained to adhere to SOPs and will be monitored for high-quality performance.

Any new use of these samples will require prospective IRB review and approval. Access to these samples will only be granted following IRB approval of an additional protocol, granting the rights to use the material.

If at any time, a patient withdraws from the study and does not wish for their existing samples to be utilized, the individual must provide a written request. Following receipt of this request, the samples will be destroyed (or returned to the patient, if so requested), and reported as such to the IRB. Any samples lost (in transit or by a researcher) or destroyed due to unknown sample integrity (i.e., broken freezer allows for extensive sample thawing, etc.) will be reported as such to the IRB.

10 STUDY CALENDAR

Baseline evaluations are to be conducted within 1 week prior to start of protocol therapy unless otherwise indicated. Patients may be registered onto protocol based on labs done within 7 days prior to entry onto study. If there is a clinical deterioration prior to day -7, repeat chemistries. Then document stability of labs with repeat chemistries 48 hours later, prior to dosing.

Repeat labs within 3 days prior to Cycle 1 Day 1. Labs need to be obtained prior to the start of each cycle (can be done up to 3 days before start of a new cycle).

Scans and x-rays must be performed within 28 days prior to the start of therapy.

	Pre-Study	C1 D-7	C1 D-6	C1 Wk 1	C1 Wk 2	C1 Wk 3	C2 on Wk 1	C2 on Wk 2	C2 on Wk 3	Off Treatment
Belinostat[a]		X		X			X			
Informed consent	X									
Demographics	X									
Medical history	X									
Child-Pugh classification (CPC)	X									
Concurrent meds[m]	X[m]	X[m]----------X[m]								
Physical exam	X	X					X			X
Vital signs	X	X					X			X
Height	X									
Weight	X	X					X			X
Performance Status	X	X					X			X
CBC w/diff, plts	X	X[d]		X[d]	X[d]	X[d]	X			X
Serum chemistry[b]	X	X[d]		X[d]	X[d]	X[d]	X			X
EKG[e]	X			X			X			
AE evaluation		X----------X								X
Tumor measurements	X	Tumor measurements are repeated every 2 cycles (about every 6 weeks). Documentation (radiologic) must be provided for patients removed from study for progressive disease.								X
Serum Magnesium[f]	X[f]	X[f]								
B-HCG	X[c]									
PT*/INR/aPTT*[g]	X									
Correlative studies[h]		X	X							
HepBsAg,HepBcAb, HepBsAb, HepBeAb[i,k]	X									
COBAS TaqMan[i,l]	X									
anti-HCV[j,k]	X									
HCV-RNA[j,l]	X									

a: Belinostat 400 mg/m^2 administered Day -7 (Cycle 1 only) and at dose assigned on Day 1-5 of each cycle.
b: Albumin, alkaline phosphatase, total and fractionated bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium.
c: Serum pregnancy test (women of childbearing potential).
d: Weekly during Cycle 1 and at the beginning of each cycle (up to 3 days before start of new cycle) for the rest of the study. If AEs are observed, these can be done more frequently at the discretion of the local PI.
e: EKG will be done pre-study, on Cycle 1 Day 5 within 5 hours after the dose, and prior to the dose at the beginning of Cycle 2. If QTc prolongation is observed, EKG will be done daily until QTc returns to < 500 msec.
f: Pre-cycle, Cycle 1 and as clinically indicated.
g: PT*/INR/aPTT* is required to be checked at baseline in all patients. Since belinostat might interact with CYP 450, patients on Coumadin should have their PT/INR monitored carefully by their local physicians.

* = as clinically indicated. h: Blood samples for correlative studies will be collected from all patients on Cycle 1 D-7 before the administration of belinostat, 15 and 25 minutes after starting infusion, and then at the following time points after the end of infusion: 5, 10, 15, 30, 60, 90 minutes, 2, 4, 6, 8, and 24 hours (D-6). i: For patients with hepatocellular carcinoma secondary to hepatitis B. j: For patients with hepatocellular carcinoma secondary to hepatitis C. k: Results may be from within 3 months before starting on study. l: Results must be from within 1 month before starting on study. M Particular attention must be paid to medications which may prolong the QTc interval (Appendix C) and agents that interact with CYP450 isoenzymes (Appendix D).

11 MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

Although response is not the primary endpoint of this trial, patients with measurable disease will be assessed by standard criteria. For the purposes of this study, patients should be reevaluated every 2 cycles (approximately 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.

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).[30] 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.

Lymphoma response will be measured using the International Workshop Lymphoma Response Criteria.[31]

11.1.1 Definitions

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

Evaluable for objective response. Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. 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 therapy, and have had their disease re-evaluated

will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

11.1.2 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, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.

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.

11.1.3 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).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with

CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. 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.

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

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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.

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

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

11.1.4 Response Criteria

11.1.4.1 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

11.1.4.2 **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 review panel (or Principal Investigator).

11.1.4.3 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.

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 evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

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

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 as 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

11.1.5 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.

11.2 Antitumor Effect – Lymphomas

Response and progression will be evaluated in this study using the International Working Group recommendations.[32]

11.2.1 CT Criteria of Nodal Involvement

Lymph nodes should be considered abnormal if the long axis is more than 1.5 cm regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if its short axis is more than 1.0. Lymph nodes 1.0 x 1.0 cm will not be considered as abnormal for relapse or progressive disease.

11.2.2 Complete Remission (CR)

1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.

2. In lymphoma that is FDG-avid prior to protocol treatment, a post-treatment residual mass of any size is permitted as long as it is PET negative.

3. For FDG negative or variably FDG-avid lymphomas or if PET scan prior to therapy not done or results not known, all lymph nodes and nodal masses must have regressed on CT to normal size (1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy. Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to 1.0 cm in their short axis after treatment.)

4. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies. Nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.

5. If the bone marrow was involved by lymphoma before treatment, the infiltrate must have cleared on repeat bone marrow biopsy. The biopsy sample on which this determination is made must be adequate (with a goal of > 20 mm unilateral core). If the sample is indeterminate by morphology, it should be negative by immunohistochemistry. A sample that is negative by immunohistochemistry but that demonstrates a small population of clonal lymphocytes by flow cytometry will be considered a CR until data become available demonstrating a clear difference in patient outcome.

11.2.3 CRu (Unconfirmed Complete Response)

The use of the above definition for CR and that below for PR eliminates the category of CRu.

11.2.4 Partial Remission (PR)

1. At least a 50% decrease in sum of the product of the diameters (SPD) of up to six of the largest dominant nodes or nodal masses. These nodes or masses should be selected according to all of the following: they should be clearly measurable in at least 2 perpendicular dimensions; if possible they should be from disparate regions of the body; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

2. No increase should be observed in the size of other nodes, liver, or spleen.

3. Splenic and hepatic nodules must regress by 50% in their SPD or, for single nodules, in the greatest transverse diameter.

4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.

5. Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified (e.g., large-cell lymphoma or small neoplastic B cells). Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders. When the bone marrow was involved before therapy

and a clinical CR was achieved, but with no bone marrow assessment after treatment, patients should be considered partial responders.

6. No new sites of disease should be observed.

7. Typically FDG-avid lymphoma: for patients with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.

8. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In patients with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

11.2.5 Stable Disease (SD)

1. A patient is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).

2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for patients without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size (> 50%) of the previous lesions on the posttreatment CT scan.

11.2.6 Relapsed Disease (after CR)/Progressive Disease (after PR, SD)

1. Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size. Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

2. At least a 50% increase from nadir in the SPD of any previously involved nodes, or in a single involved node, or the size of other lesions (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0 cm must increase by 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.

3. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.

4. Lesions should be PET positive if observed in a typical FDG-avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT). Measurable extra-nodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (e.g., pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

12 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for adverse event reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will be monitored by the Clinical Trials Monitoring Service (CTMS). Information on CTMS reporting is available at http://www.theradex.com/CTMS/ctmsmenu.htm. Data will be submitted to CTMS at least once every 2 weeks on the NCI/DCTD case report form or the electronic case report form (ACES). CTEP will arrange for a bi-weekly toxicity report to be generated by Theradex, and this report will be provided to the Principal Investigator, all Co-Investigators, and the Organ Dysfunction Working Group for the purposes of monitoring and coordination of this multicenter trial. The final study report should contain all raw data collected during the trial including the case report forms as well as all clinical, laboratory, pharmacokinetic, and pharmacodynamic data collected. This report will be made available to the FDA as well as all members of the Organ Dysfunction Working Group.

12.1.2 Responsibility for Data Submission

Study participants are responsible for submitting CTMS data and/or data forms to the Coordinating Center quarterly to allow time for Coordinating Center compilation, Principal Investigator review, and timely submission to CTEP (see Section 12.1.1.). For trials monitored by CTMS, the monthly data submission to CTEP from Theradex should be copied to the Coordinating Center.

The Coordinating Center is responsible for compiling and submitting CTMS data to CTEP for all participants and for providing the data to the Principal Investigator for review.

12.2 Data Monitoring and Safety Plan

A mandatory conference call will take place every other week on Friday at 1300 (Eastern Time) unless unforeseen events require postponement or cancellation (Appendix I). The call will update participants on the current status of the trial and will include investigators from all participating centers, CTEP, and representatives from TopoTarget. At this time, any serious toxicities encountered will be discussed and appropriate action taken, and issues relating to the protocol, treatment, management, or other matters of importance that arise during the conduct of the study will be discussed. Between these regularly scheduled conference calls, unusual toxicities may be discussed among the Principal Investigator and CTEP senior investigators; however, all participants will routinely be updated on such calls via e-mail.

All SAEs will be reported through CTEP-AERS to CTEP, to the Coordinating Center PI at NCI, and forwarded to the IRB per Section 7. In all cases where the dose of the study treatment has been reduced/modified or the patient withdrawn due to unusual or unusually severe toxicity considered related to the study treatment, the investigator must contact and inform the Coordinating Center PI. All sites will be monitored by the CTEP drug monitor who will receive data from all participating sites.

Data will be monitored regularly by the principal investigator in order to identify significant toxicity trends. Any new significant finding that may affect the patient's willingness to continue in the study will be shared with patients. The Coordinating Center is responsible for establishing bimonthly conference calls between participating sites to discuss protocol issues.

Confidentiality will be maintained as much as possible, consistent with applicable regulations. Names of participants or identifying material will not be released without patient permission, except when such release is required by law. No patient's name or identifying information will be released in any publication or presentation. Records are maintained according to current legal requirements, and are made available for review according to the requirements of the FDA or other authorized user, only under guidelines established by the Federal Privacy Act.

12.3 Multi-Institutional Guidelines

This protocol will open initially at the NCI. The NCI IRB will be notified once the participating centers' IRBs have approved the study to open.

12.3.1 IRB Approvals

As the Coordinating Center for a trial, it is the PI's responsibility to ascertain that no patients are entered on the trial at a participating institution without full IRB approval. Thus, the NCI IRB must approve the addition of each participating institution to the protocol and will require a copy of the local IRB approval from each participating institution before NCI IRB approval will be granted.

The PI will provide the NCI IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NCI IRB.

12.3.2 Amendments and Consents

The PI will provide the NCI IRB with copies of all amendments, consents, and approvals from each participating institution.

12.3.3 Data Collection

The investigators will be responsible for the collection, maintenance, and quality control of the study data. All data collected for each study subject will be entered into the Cancer Central Clinical Database (C3D), an NCI electronic case report form/database, every 2 weeks. Once a participating site has received IRB approval, data managers and research nurses will receive training on the C3D database. Each participating site must electronically send the names and office contact information of all of the intended C3D users to NCI, DTC research nurse. This information will be emailed to the C3D programmers for the scheduling of individualized virtual training. The database programmers will coordinate the logistics of the virtual training with each site, and assign a user identification and password with the completion of training. Once the intended users are trained, participating sites will be able to enroll patients and enter the data remotely into the web-based C3D system. The electronic C3D instruction manual serves as a resource to assist with data entry into the NCI, CCR's C3D electronic case report forms. Each site investigator is responsible for maintaining all source documentation related to the study, including any films, tracings, computer discs or tapes. NCI will be responsible for data management, data analysis, and reporting. Data collection forms are provided for the participating institutions (Appendices J and K). Required data include, not exclusively: prior disease-related therapies, with dates, disease type, stage, disease sites, with measurements, and concurrent medications.

12.3.4 Data and Center Audits

Audits will be conducted yearly to ensure data integrity and provide quality control. These audits will be conducted by the NCI research team. Selected patient charts should be audited as well as the participating institution's Standard Operating Procedures (SOP) at the time of the visit. Data from participating institutions should be available when the protocol is audited at the NCI.

12.3.5 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Principal Investigator and the Coordinating Center (NCI, DTC) and the procedures for auditing are presented in Appendix E.

- The Principal Investigator/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov).

12.4 Clinical Trials Agreement (CTA)

The agent(s), supplied by CTEP, DCTD, NCI, used in this protocol is/are provided to the NCI under a Collaborative Agreement (CTA) between the Topo Target [hereinafter referred to as "Collaborator(s)"] and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of Agent(s) in this study:

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

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

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

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

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

3. Clinical Trial Data and Results and Raw Data developed under a collaborative agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate. All data made available will comply with HIPAA regulations.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

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

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

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   9609 Medical Center Drive RM 5-W
   Rockville, MD 20850 (fed ex)
   Phone: 240-276-6580
   Fax: 240-276-7894
   E-mail: ncicteppubs@mail.nih.gov

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

13 STATISTICAL CONSIDERATIONS

This is a Phase I trial using a design including 4 cohorts of patients with varying degrees of hepatic dysfunction, including one group with normal hepatic function (see Section 5.1.1). The study incorporates a 3+3 design. The dose recommended for cohorts with greater liver dysfunction cannot be greater than the dose for cohorts of lesser dysfunction (see Section 5.1.5). Furthermore, the highest dose to be explored is no greater than the recommended dose for patients with normal liver function. These restrictions will compensate in part for patient

heterogeneity and yield more accurate final recommended doses in liver dysfunction groups. Further rules for dose escalation and MTD determination are given in Sections 5.1 and 5.2.

Patients in cohort 1 are included in this study to obtain PK data in the same manner as for the patients with liver dysfunction. This group will also be followed for toxicity. Occasionally a patient consented for a group with liver dysfunction will present with normal liver function tests on the day of treatment initiation. These patients may be entered into cohort 1 on a case-by-case basis.

Toxicity will be graded according to the NCI CTCAE v4.0 and relationship to the study drug; results will be tabulated by liver dysfunction group. All patients who receive any amount of belinostat will be evaluable for toxicity, but patients who receive other than the prescribed dose and do not experience a DLT will be considered inevaluable for DLT. Patients who are not evaluable for DLT will be replaced.

The PK variables described in Section 9.1 will be tabulated and descriptive statistics calculated for each function group. Geometric means and coefficients of variation will be presented for C_{max} and AUC_{INF} for each group.

In addition, indirect bilirubin levels will be evaluated to see if there is a correlation between those results and toxicity or activity of belinostat.

13.1 Sample Size/Accrual Rate

A minimum of 2 and a maximum of 6 patients will be accrued in each liver dysfunction cohort (2-4) at each dose level, and 12 patients will be entered at the recommended dose level in cohort 1. MTD will not be established for the normal cohort as that is already known. Patients in this cohort are being enrolled to obtain PK data in the same manner as for the patients with liver dysfunction. Three additional patients will be accrued to the MTD levels (following establishment of MTD for that cohort in the first 6 patients at that dose level) for each liver dysfunction cohort to allow additional information to be gained at these levels. Therefore, the minimum number of patients will be 24 patients. The maximum would include the 12 patients in cohort 1, 6 patients for all other non-MTD levels (up to 6 such), and 9 patients for the MTD levels (3 such), bringing the total to 75 patients. We do not expect all dose levels to have 6 patients and recognize that some patients may need to be replaced if they are not evaluable based on protocol guidelines. As long as < 33% of the patients treated at a given dose level experience a DLT, that dose level will be considered the MTD.

The estimated monthly accrual is 4 patients/month, and the accrual ceiling for this trial is 80 patients.

13.2 Stratification Factors

Patients will be stratified according to the level of hepatic dysfunction as described in Section 5.1.1. Dose escalation and MTD determination will be performed separately for each stratum.

14 HUMAN SUBJECTS PROTECTIONS

14.1 Rationale for Subject Selection

This study will be open to all individuals regardless of gender, ethnicity, or race, provided that the aforementioned inclusion and exclusion criteria are met. Patients for this study will be recruited through internal referral, our physician referral base, and through various cancer information hotlines (i.e., Clinical Studies Support Center, 1-800-4Cancer). To date, there is no information that suggests that differences in drug metabolism or effect on tumor would be expected in one ethnic group compared to another. Efforts will be made to extend accrual to each representative population, but a balance must be struck between participant safety considerations and limitations on the number of individuals exposed to potentially ineffective treatments on the one hand and the need to explore racial/ethnic aspects of clinical research on the other hand. If differences in outcome that correlate to ethnic identity are noted, a follow-up study may be written to investigate those differences more fully.

Due to lack of knowledge of the effects of belinostat on the fetus or infants, as well as the possibility of teratogenic effects, pregnant and nursing women will be excluded from this trial. Patients with unstable or serious medical conditions are excluded due to the possibility that belinostat may worsen their condition and the likelihood that the underlying condition may obscure the attribution of adverse events with respect to belinostat. HIV-positive patients on combination antiretroviral therapy are excluded from the study because of possible PK interactions with belinostat.

14.2 Participation of Children

Children aged <18 years are excluded because of the lack of safety data of the compound in this population. Appropriate studies in the pediatric age group may be undertaken in the future.

14.3 Evaluation of Benefits and Risks/Discomforts

Patients will receive evaluation and treatment of their malignancy as a result of participating in this trial. All the medications, tests, hospitalizations, and physician services during this trial within the NIH will be free of charge to the participant. Imaging studies may help determine the extent of disease and or identify lesion not detected by conventional modalities. The trial will help investigators learn the effects of the study medication, but may or may not be helpful for a specific patient. The study treatment may offer temporary control of the disease, but is not

curative by this protocol. Benefit cannot be promised nor can the chance of benefit be accurately predicted. The risks and discomforts of the tumor biopsies will be slight pain, as well as the small possibility of bleeding or infection. Alternative approaches other than entering this trial, including supportive care only, if it is available, will also be discussed before the verbal and written consent regarding the risk and benefits and the treatment requirements of this trial.

14.3.1 Alternative Approaches or Treatments

There are no effective alternative therapies. Other investigational agents could be employed, or the patient may elect to be treated for symptomatic control alone or with agents of marginal or unknown clinical benefit.

14.3.2 Procedure for Protecting Against or Minimizing Potential Risks

All care will be taken to minimize side effects, but they can be unpredictable in nature and severity. This study may involve risks to patients, which are currently unforeseeable. All patients will be monitored for side effects from taking study medication and from undergoing research-related procedures. If patients suffer any physical injury as a result of the participation in this study, immediate medical treatment is available at the Clinical Center, National Cancer Institute, Bethesda, Maryland. Although no compensation is available, any injury will be evaluated and treated in keeping with the benefits or care to which patients are entitled under applicable regulations.

14.4 Risks/Benefits Analysis

There may or may not be any clinical benefit to a patient from participation in this trial. Their participation will benefit future cancer patients. Potential risks include the possible occurrence of any of a range of side effects that are listed in the consent document. Clinical and laboratory data gathered in this trial will be analyzed frequently. Any new or significant finding(s) found during the course of the research that may affect a patient's willingness to participate further will be shared and explained to each participant.

14.5 Consent Process and Documentation

An associate or principal investigator on the trial will inform patients of the purpose, alternatives, drug administration plan, research objectives and follow-up of this trial. The patient will be provided an IRB-approved consent for review and signature and his/her questions will be answered. After a decision is made to enroll into the study, a signature will be obtained from the patient. The original signed consent goes to Medical Records; a copy is placed in the research record.

All patients must have a signed informed consent form and an on-study (confirmation of eligibility) form filled out and signed by a participating investigator before entering on study.

For NCI only: adults unable to give consent are excluded from enrolling in the protocol. However, re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation, all subjects ≥ age 18 will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study. Note: The PI or AI will contact the NIH Ability to Consent Assessment Team for evaluation. For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MEC Policy 87-4 for appointing a surrogate decision maker for adult subjects who are (a) decisionally impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

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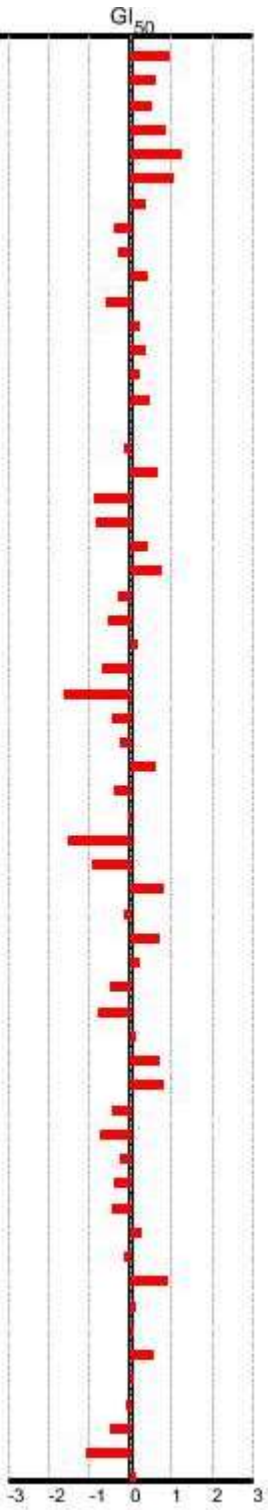
APPENDIX A: GI50 MEAN GRAPH FOR NSC 726630 (BELINOSTAT)

Data from October 2009; average GI_{50} over all cell lines is 1.78E-7.

Cell Panel	Cell Line	Log GI_{50}
Leukemia	CCRF-CEM	-7.7
	HL-60(TB)	-7.4
	K-562	-7.2
	MOLT-4	-7.6
	RPMI-8226	-8.0
	SR	-7.8
Non-Small Cell Lung	A549/ATCC	-7.1
	EKVX	-6.4
	HOP-62	-6.5
	HOP-92	-7.1
	NCI-H226	-6.2
	NCI-H23	-7.0
	NCI-H322M	-7.1
	NCI-H460	-6.9
	NCI-H522	-7.2
Colon	COLO 205	-6.8
	HCC-2998	-6.6
	HCT-116	-7.4
	HCT-15	-5.9
	HT29	-5.9
	KM12	-7.1
	SW-620	-7.5
Central Nervous System	SF-268	-6.5
	SF-295	-6.2
	SF-539	-6.9
	SNB-19	-6.1
	SNB-75	-5.2
	U251	-6.3
Melanoma	LOX IMVI	-6.5
	MALME-3M	-7.4
	M14	-6.4
	MDA-MB-435	-6.7
	SK-MEL-2	-5.2
	SK-MEL-28	-5.8
	SK-MEL-5	-7.5
	UACC-257	-6.6
	UACC-62	-7.4
Ovarian	IGROV1	-6.9
	OVCAR-3	-6.3
	OVCAR-4	-6.0
	OVCAR-5	-6.8
	OVCAR-8	-7.5
	NCI/ADR-RES	-7.5
	SK-OV-3	-6.3
Renal	786-0	-6.0
	A498	-6.5
	ACHN	-6.4
	CAKI-1	-6.3
	RXF 393	-7.0
	SN12C	-6.6
	TK-10	-7.6
	UO-31	-6.9
Prostate	PC-3	-6.8
	DU-145	-7.3
Breast	MCF7	-6.8
	MDA-MB-231/ATCC	-6.7
	HS 578T	-6.3
	BT-549	-5.7
	T-47D	-6.8



APPENDIX B: 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.

APPENDIX C: MEDICATIONS KNOWN TO PROLONG THE QT INTERVAL AND/OR INDUCE TORSADES DE POINTES

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired long QT syndrome, known as drug-induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsades de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

Table 1. Group 1 Drugs That are Generally Accepted by Authorities to Have a Risk of Causing TdP*

Drug (generic names)	Drug class (clinical usage)	Comments
Albuterol (by parenteral administration)	Bronchodilator (asthma)	Inhaled albuterol at normal doses acceptable
Amiodarone	Anti-arrhythmic (heart rhythm)	F >M, TdP cases in literature
Arsenic trioxide	Anti-cancer (leukemia)	TdP cases in literature
Bepridil	Anti-anginal (heart pain)	F >M
Chlorpromazine	Anti-psychotic/anti-emetic (schizophrenia/nausea)	TdP cases in literature
Chloroquine	Anti-malaria (malaria infection)	
Disopyramide	Anti-arrhythmic (heart rhythm)	F >M
Dofetilide	Anti-arrhythmic (heart rhythm)	
Droperidol	Sedative/hypnotic (anaesthesia adjunct)	TdP cases in literature
Erythromycin	Antibiotic/GI stimulant (infection/GI motility)	F >M
Halofantrine	Anti-malarial (malaria infection)	F >M
Haloperidol	Anti-psychotic (schizophrenia, agitation)	
Ibutilide	Anti-arrhythmic (heart rhythm)	F >M
Mesoridazine	Anti-psychotic (schizophrenia)	
Methadone	Opiate agonist (pain control/ narcotic dependence)	F >M
Pentamidine	Anti-infective (pneumocystic pneumonia)	F >M
Pimozide	Anti-psychotic (Tourette's tics)	F >M, TdP cases in literature
Procainamide	Anti-arrhythmic (heart rhythm)	
Quinidine	Anti-arrhythmic (abnormal heart rhythm)	F >M
Sotalol	Anti-arrhythmic (heart rhythm)	F >M
Sparfloxacin	Antibiotic (bacterial infection)	
Thioridazine	Anti-psychotic (schizophrenia)	

*Concomitant use of these drugs is **not** allowed during the study or within 2 weeks of study entry. These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment.

Table 2. Group 2 Drugs That in Some Reports may be Associated With TdP but at This Time Lack Substantial Evidence of Causing It*

Drug (brand names)	Drug class (clinical usage)	Comments
Amantadine	Dopaminergic/anti-viral/anti-infective (Parkinson's disease)	
Amitriptyline	Tricyclic anti-depressant (depression)	
Amoxapine	Tricyclic anti-depressant (depression)	
Azithromycin	Antibiotic (bacterial infection)	
Citalopram	Anti-depressant (depression)	
Clarithromycin	Antibiotic (bacterial infection)	TdP cases in literature
Clomipramine	Tricyclic antidepressant (depression)	
Chloral hydrate	Sedative (sedation/insomnia)	
Clozapine	Anti-psychotic (schizophrenia)	
Desipramine	Tricyclic anti-depressant (depression)	TdP cases in literature
Dolasetron	Anti-nausea (nausea and vomiting)	
Doxepin	Anti-depressant (depression)	TdP cases in literature
Felbamate	Anti-convulsant (seizures)	
Flecainide	Anti-arrhythmic (heart rhythm)	Association not clear
Fluconazole	Anti-fungal (fungal infection)	
Fluoxetine	Anti-depressant (depression)	Association not clear
Foscarnet	Antiviral (HIV infection)	
Fosphenytoin	Anticonvulsant (seizures)	
Gatifloxacin	Antibiotic (bacterial infection)	
Gemifloxacin	Antibiotic (bacterial infection)	
Granisetron†	Anti-nausea (nausea and vomiting)	
Imipramine	Anti-depressant (depression, pain, other)	TdP cases in literature
Indapamide	Diuretic (stimulates urine & salt loss)	TdP cases in literature, QT in animals
Isradipine	Anti-hypertensive (high blood pressure)	
Levofloxacin	Antibiotic (bacterial infection)	Association not clear
Lithium	Anti-mania (bipolar disorder)	

Drug (brand names)	Drug class (clinical usage)	Comments
Mexiletine	Anti-arrhythmic (abnormal heart rhythm)	
Moexipril/HCTZ	Anti-hypertensive (high blood pressure)	
Moxifloxacin	Antibiotic (bacterial infection)	
Nicardipine	Anti-hypertensive (high blood pressure)	
Nortriptyline	Tricyclic antidepressant (depression)	
Octreotide	Endocrine (acromegaly/ carcinoid diarrhoea)	
Ofloxacin		
Ondansetron†	Anti-emetic (nausea and vomiting)	
Paroxetine	Anti-depressant (depression)	
Protriptyline	Tricyclic antidepressant (depression)	
Quetiapine	Anti-psychotic (schizophrenia)	
Risperidone	Anti-psychotic (schizophrenia)	
Salmeterol	Sympathomimetic (asthma, COPD)	
Sertraline	Antidepressant (depression)	Association not clear
Solifenacin	Muscarinic receptor antagonist (treatment of overactive bladder)	
Tacrolimus	Immune suppressant	TdP cases in literature
Tamoxifen	Anti-cancer (breast cancer)	
Telithromycin	Antibiotic (bacterial infection)	
Tizanidine	Muscle relaxant	
Trimipramine	Tricyclic antidepressant (depression)	
Vardenafil	Phosphodiesterase inhibitor (vasodilator)	
Venlafaxine	Antidepressant (depression)	
Voriconazole	Anti-fungal (fungal infection)	
Ziprasidone	Anti-psychotic (schizophrenia)	

*Concomitant use of these drugs will be allowed at the discretion of the PI. In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes. Patients who are receiving a drug that has a risk of QTc prolongation are excluded if QTc is ≥460 msec.

†Granisetron and ondansetron are acceptable antiemetics in this study. In clinical use, QT interval changes do not exceed 15 msec, and consequently, the potential for induction of arrhythmias is low.[33]

APPENDIX D: CYP450 INTERACTIONS

CTEP List of drugs that may have potential CYP3A4 interactions

CYP3A4 Substrates

Albuterol	Dihydroergotamine	Isosorbide mononitrate	Quinidine
Alfentanil	Diltiazem	Isradipine	Rabeprazole
Alprazolam	Disopyramide	Itraconazole	Ranolazine
Amiodarone	Docetaxel	Ketamine	Repaglinide
Amlodipine	Doxepin	Ketoconazole	Rifabutin
Amprenavir	Doxorubicin	Lansoprazole	Ritonavir
Aprepitant	Doxycycline	Letrozole	Salmeterol
Aripiprazole	Efavirenz	Levonorgestrel	Saquinavir
Atazanavir	Eletriptan	Lidocaine	Sibutramine
Atorvastatin	Enalapril	Losartan	Sildenafil
Benzphetamine	Eplerenone	Lovastatin	Simvastatin
Bisoprolol	Ergoloid mesylates	Medroxyprogesterone	Sirolimus
Bortezomib	Ergonovine	Mefloquine	Spiramycin
Bosentan	Ergotamine	Mestranol	Sufentanil
Bromazepam	Erythromycin	Methadone	Sunitinib
Bromocriptine	Escitalopram	Methylergonovine	Tacrolimus
Budesonide	Estradiol	Methysergide	Tamoxifen
Buprenorphine	Estrogens, conj.,	Miconazole	Tamsulosin
Buspirone	synthetic	Midazolam	Telithromycin
Busulfan	Estrogens, conj., equine	Miglustat	Teniposide
Carbamazepine	Estrogens, conj.,	Mirtazapine	Tetracycline
Cerivastatin	esterified	Modafinil	Theophylline
Chlordiazepoxide	Estrone	Montelukast	Tiagabine
Chloroquine	Estropipate	Moricizine	Ticlopidine
Chlorpheniramine	Ethinyl estradiol	Nateglinide	Tipranavir
Cilostazol	Ethosuximide	Nefazodone	Tolterodine
Cisapride	Etoposide	Nelfinavir	Toremifene
Citalopram	Exemestane	Nevirapine	Trazodone
Clarithromycin	Felbamate	Nicardipine	Triazolam
Clobazam	Felodipine	Nifedipine	Trimethoprim
Clonazepam	Fentanyl	Nimodipine	Trimipramine
Clorazepate	Flurazepam	Nisoldipine	Troleandomycin
Cocaine	Flutamide	Norethindrone	Vardenafil
Colchicine	Fluticasone	Norgestrel	Venlafaxine
Conivaptan	Fosamprenavir	Ondansetron	Verapamil
Cyclophosphamide	Gefitinib	Paclitaxel	Vinblastine
Cyclosporine	Haloperidol	Pergolide	Vincristine
Dantrolene	Ifosfamide	Phencyclidine	Vinorelbine
Dapsone	Imatinib	Pimozide	Zolpidem
Dasatinib (1)	Indinavir	Pipotiazine	Zonisamide
Delavirdine	Irinotecan	Primaquine	Zopiclone
Diazepam	Isosorbide	Progesterone	
	Isosorbide dinitrate	Quetiapine	

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

CYP2C8 Substrates

Role for CYP2C8
Major role
Amiodarone
Amodiaquine
Arachidonic acid (2C9, 2J2)
Cerivastatin (3A4 minor)
Chloroquine (3A4 minor)
Paclitaxel (3A4)
Repaglinide (3A4 minor)
Retinoic acid (2C9)
Rosiglitazone (3A4 minor)
Tazarotenic acid
Troglitazone (3A4 minor)
Intermediate role
Diclofenac
Fluvastatin (2C9, 3A4)
Ibuprofen (2C9)
Methadone (3A4, 2D6, 2B6)
Morphine (3A4)
Minor role
Carbamazepine (3A4 major)
Cyclophosphamide (2A6, 2B6, 2C9, 2C19, 3A)
Dapsone (2C9 major)
Ifosfamide (2A6, 2B6, 2C9, 2C19, 3A4)
Torsemide (2C9 major)
Verapamil (3A4 major)
Zopiclone (3A4 major)

Other CYPs that contribute to metabolism are given in parenthesis.

CYP2C9 Substrates

diclofenac	losartan	fluoxetine
ibuprofen	irbesartan	fluvastatin
lornoxicam	glyburide	glyburide
meloxicam	glibenclamide	nateglinide
S-naproxen_Nor	glipizide	phenytoin-4-OH2
piroxicam	glimepiride	rosiglitazone
suprofen	tolbutamide	tamoxifen
tolbutamide	amitriptyline	torsemide
glipizide	celecoxib	S-warfarin

Additional information for drug interactions with cytochrome P450 isoenzymes can be found at http://medicine.iupui.edu/flockhart/.

APPENDIX E: CTEP MULTICENTER GUIDELINES

If an institution wishes to collaborate with other participating institutions in performing a CTEP sponsored research protocol, then the following guidelines must be followed.

Responsibility of the Protocol Chair

- The Protocol Chair will be the single liaison with the CTEP Protocol and Information Office (PIO). The Protocol Chair is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Protocol Chair. There will be only one version of the protocol, and each participating institution will use that document. The Protocol Chair is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Protocol Chair is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements to CTEP are the responsibility of the Protocol Chair.
- The Protocol Chair is responsible for the timely review of adverse events to assure safety of the patients.
- The Protocol Chair will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- Each participating institution will have an appropriate assurance on file with the Office for Human Research Protection (OHRP), NIH. The Coordinating Center is responsible for assuring that each participating institution has an OHRP assurance and must maintain copies of IRB approvals from each participating site.
- Prior to the activation of the protocol at each participating institution, an OHRP form 310 (documentation of IRB approval) must be submitted to the CTEP PIO.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Protocol Chair.
- The Coordinating Center will maintain documentation of adverse event reports. There are two options for adverse event reporting: (1) participating institutions may report directly to CTEP with a copy to the Coordinating Center, or (2) participating institutions report to the Coordinating Center who in turn report to CTEP. The Coordinating Center will submit adverse event reports to the Protocol Chair for timely review.

- Audits may be accomplished in one of two ways: (1) source documents and research records for selected patients are brought from participating sites to the Coordinating Center for audit, or (2) selected patient records may be audited on-site at participating sites. If the NCI chooses to have an audit at the Coordinating Center, then the Coordinating Center is responsible for having all source documents, research records, all IRB approval documents, NCI Drug Accountability Record forms, patient registration lists, response assessments scans, x-rays, etc. available for the audit.

Inclusion of Multicenter Guidelines in the Protocol

- The protocol must include the following minimum information:
  - The title page must include the name and address of each participating institution and the name, telephone number and e-mail address of the responsible investigator at each participating institution.
  - The Coordinating Center must be designated on the title page.
  - Central registration of patients is required. The procedures for registration must be stated in the protocol.
  - Data collection forms should be of a common format. Sample forms should be submitted with the protocol. The frequency and timing of data submission forms to the Coordinating Center should be stated.
  - Describe how adverse events will be reported from the participating institutions, either directly to CTEP or through the Coordinating Center.
  - Describe how Safety Reports and Action Letters from CTEP will be distributed to participating institutions.

Agent Ordering

- Except in very unusual circumstances, each participating institution will order DCTD-supplied investigational agents directly from CTEP. Investigational agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO.

APPENDIX F: PHARMACOKINETIC SAMPLE ACQUISITION FORM

INSTRUCTIONS: This form should be completed as required per protocol. Information in the upper box must be completed for this form to be accepted. Do not leave any entries blank. Enter all times in 24-hour format. Enter - 1 to indicate that an answer is unknown, unobtainable, not applicable, or not done. Highlight or circle amended data. **Include ORIGINAL form with sample shipment, retain a copy for your records**.

Patient's Initials: _____
Patient Accession Number: _____
Institution:

DAY -7 Date Belinostat administered: (mm/dd/yy) ⌴⌴/⌴⌴/⌴⌴

DOSING INFORMATION

Belinostat Dose (mg/m^2) ⌴⌴⌴ BSA (m^2) ⌴.⌴⌴

Belinostat Dose (mg) ⌴⌴⌴

Time Belinostat Started: (hh:mm) ⌴⌴:⌴⌴

Each timed sample will be noted with corresponding number (1-14) for labeling purposes

BLOOD SAMPLES REQUIRED:

#		Projected Time Obtained (hh:mm)	Actual Time Obtained (hh:mm)	Problems? Specify
1	Pre-Belinostat (B)	⌴⌴:⌴⌴	⌴⌴:⌴⌴	
2	15 min into infusion of B	⌴⌴:⌴⌴	⌴⌴:⌴⌴	
3	25 min into infusion of B	⌴⌴:⌴⌴	⌴⌴:⌴⌴	
4	5 min after end of infusion of B	⌴⌴:⌴⌴	⌴⌴:⌴⌴	
5	10 min after end of infusion of B	⌴⌴:⌴⌴	⌴⌴:⌴⌴	
6	15 min after end of infusion of B	⌴⌴:⌴⌴	⌴⌴:⌴⌴	
7	30 min after end of infusion of B	⌴⌴:⌴⌴	⌴⌴:⌴⌴	
8	1 h after end of infusion of B	⌴⌴:⌴⌴	⌴⌴:⌴⌴	

#		Projected Time Obtained (hh:mm)	Actual Time Obtained (hh:mm)	Problems? Specify
9	1.5 h after end of infusion of B	␣␣:␣␣	␣␣:␣␣	
10	2 h after end of infusion of B	␣␣:␣␣	␣␣:␣␣	
11	4 h after end of infusion of B	␣␣:␣␣	␣␣:␣␣	
12	6 h after end of infusion of B	␣␣:␣␣	␣␣:␣␣	
13	8 h after end of infusion of B	␣␣:␣␣	␣␣:␣␣	
14	24 h after end of infusion of B	␣␣:␣␣	␣␣:␣␣	

SHIPPING INFORMATION:

SHIP TO: **Clinical Pharmacology Analytical Facility**
Attention of Dr. Jan H. Beumer
UPCI Hillman Research Pavilion, G.28
5117 Centre Avenue
Pittsburgh, PA 15213

***Prior to shipment of samples, please contact Clinical Pharmacology Analytical Facility by calling (412) 623-1213 or (412) 623-3248 or by sending a fax to Dr. Beumer at (412) 623-1212.**

Condition of sample when shipped (1-frozen, 2-thawed) ␣

Date sample shipped: (mm/dd/yy) ␣␣/␣␣/␣␣

Shipper's name: _____ E-mail address or phone no.: _____

APPENDIX G: MULTICENTER INFORMED CONSENT TEMPLATE

Phase I Pharmacokinetic Study of Belinostat for Solid Tumors and Lymphomas in Patients with Varying Degrees of Hepatic Dysfunction

Introduction

We invite you to take part in this research study.

First, we want you to know that:

Taking part in this research study is entirely voluntary.

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with family, friends or your personal physician or other health professional.

You have been asked to take part in a clinical research study testing an experimental drug, called belinostat, because you have an advanced cancer and your liver may or may not be working properly, and the standard drugs to treat your disease are no longer effective, or it may be that no effective treatment is known for your disease.

Description of Research Study

The purpose of this study is to test the safety of belinostat at different dose levels in patients with cancer who have different degrees of liver function. Belinostat is an experimental drug that works by helping to turn on genes that control cell growth and survival that are switched off in cancer cells. This is the first study in which belinostat will be given systematically to patients with different degrees of liver function. We already know the safe dose for patients with normal liver function. Other purposes of this study are to find out what side effects occur when belinostat is given to patients with different degrees of liver function, how much belinostat is in your blood at specific times, and whether or not belinostat is effective in treating your cancer. We will compare how the patients with abnormal liver function do in comparison with patients with

normal liver function. That is the reason that a group of patients with normal liver function will also be included on this trial.

How many people will take part in this study?
Up to 80 patients will take part in this study at multiple centers across the United States. Out of this, about ___ patients will take part in this study at _____ *[name of center]*.

Has this drug been given to other people?
Belinostat has been given to about 500 patients with different types of cancer to measure its safety and how the body handles this drug. Belinostat has not been given in a formal trial to patients with cancer who have abnormal liver function to learn how these patients tolerate and respond to the drug.

What will happen if I take part in this study?
Before you begin the study
You will need to have the following examinations, tests, or procedures to find out if you can be in the study. These examinations, tests, or procedures are part of your regular cancer care and should be done by your health care team even if you do not join the study. If you have had them recently, they may not need to be repeated. This will be up to your study doctor.

If you decide that you would like to participate in this study, you will be asked to sign this consent form. You will then have the examinations, tests, and procedures listed below done to see if you can take part in the study (this is called the screening/baseline evaluation).

- **Complete medical history.**
- **Physical examination,** including height, weight, blood pressure, pulse, and temperature.
- **Standard blood tests** (requiring about 1 tablespoon of blood total), which include measurement of your white blood cells, red blood cells, platelets, blood sugar and electrolytes, how your liver and kidneys work, and how well your blood clots.
- **Urine tests:** Depending on the results of blood tests, you may be asked to give a collect your urine for 24 hours for further testing.
- **Pregnancy test:** A blood test will be done to check for pregnancy in women who are able to become pregnant.
- **EKG** to check your heart.
- **CT scans** of your chest, abdomen, and pelvis to measure your tumor(s). Other imaging tests may be done as needed.

During the Study
After you are accepted for this study and you choose to take part, you will begin taking the study drug, belinostat. Belinostat is given through a vein for 30 minutes. Belinostat will be given in cycles. Except for cycle 1, all cycles are 3 weeks long. Cycle 1 is 4 weeks long. Now, we will describe what will happen during each cycle.

For cycle 1 only, you will receive one extra dose of belinostat 1 week before the regular treatment starts (Day -7). **In each cycle,** belinostat will be given once a day for 5 days (Day 1-5).

For some study procedures we will need you to come to _____ *[name of center]*. You will also have tests performed because you are in the study to see how the study drugs are affecting your body. This will include imaging studies (for example, CT scans) every 2 cycles (about every 6 weeks) to find out if your cancer has responded.

Clinical Center Visits: We will ask that you come to _____ *[name of center]* each day you receive belinostat (6 days in cycle 1 and 5 days in all other cycles) and on other days during cycle 1 when samples are collected for research (see Study Chart). While you are at _____ *[name of center]*, we will also perform study tests and procedures to see how the study drugs are affecting your body.

Standard procedures being done because you are in this study; these may be done more often because you are in the study:

- **Clinic visit** to ask how you are feeling and to evaluate you with a physical examination at the beginning of each cycle.
- **Vital signs:** You will need to have your vital signs, including your temperature, heart rate, blood pressure, and respiratory rate, measured each time you are seen in the outpatient clinic.
- **Blood tests:** Measurement of your white blood cells, red blood cells and platelets, and measurements of your blood sugar and electrolytes and of how your liver and kidneys work will be done each time you are seen in the outpatient clinic. All of these blood tests combined will require 1-2 tablespoons (20-30 mL) of blood each time.
- **Urine test:** Depending on the results of blood tests, you may be asked to give a urine sample for testing or to collect your urine for 24 hours for further testing.
- **EKG** to check your heart on Day 5 of cycle 1, at the beginning of cycle 2, and more often if needed.
- **CT scans** or other imaging tests such as ultrasound (an examination using sound waves) or MRI (an examination using magnetic field and radio waves) that detect your tumor will be done every 2 cycles (about every 6 weeks) while you are receiving treatment. This is done so that any benefit of the treatment can be determined, and so that if your cancer is not responding to the treatment, the study team can tell you and help you move to a different treatment program (discussed further below).

Tests and procedures that are either being tested in this study or being done to see how the study is affecting your body:

- **Measurements of the drug in your blood and urine:** We will collect blood samples to measure amounts of belinostat in your blood several times during the first cycle. Because we will collect several blood draws, a thin, flexible plastic tube (called a "catheter") will be placed in your arm, and all blood samples would be taken from this tube. Using a

catheter will reduce the number of times a needle would be placed in your vein. The total amount of blood that we collect will be about 4 tablespoons (52 mL).

Patients in this study will be divided into 4 groups. You will be placed in one of these groups based on how your liver is functioning (determined from the results of the blood tests done to check your liver). Up to 12 patients with normal liver function will be included in the study. All of the patients with normal liver function will receive the same dose of belinostat. For each group of patients with abnormal liver function, 3 patients will be enrolled and will begin with a low dose of belinostat. If no serious side effects are reported, the next set of 3 patients enrolled in that group will receive a higher dose of belinostat. This will continue as long as belinostat is well tolerated, or the dose reaches the level that caused side effects in patients with normal liver function. The dose level of the study drug you receive will depend on when you enter the study, and whether patients enrolled before you had any serious side effects at their dose levels. If serious side effects are seen, the dose of the study drug may be lowered or stopped depending on the severity of the side effects.

Study Chart
The chart below shows what will happen to you while you take part in this study. The left-hand column shows the day in the cycle, and the right-hand column tells you what will happen on that day.

Day	**What to do and what will happen to you**
Before starting study drug	• Check in at Outpatient Clinic • Get routine blood tests • EKG will be done to check your heart • Pregnancy test • Have a history taken of how you feel and undergo a physical examination by a Health Care Provider • CT scan will be done
Cycle 1, Day -7	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination • Get routine blood tests • Receive belinostat through a vein for 30 minutes • Have blood samples taken for research
Cycle 1, Day -6	• Have blood samples taken for research
Cycle 1, Days 1-5	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination • Receive belinostat through a vein once a day for 30 minutes • EKG will be done on Day 5 to check your heart • Get routine blood tests
Cycle 1, Days 6-21	• Get routine blood tests once a week
Cycle 2 and onwards, Days 1-5	• Check in at Outpatient Clinic • Have a history taken of how you feel and undergo a physical examination

Day	What to do and what will happen to you
	• Get routine blood tests • Receive belinostat through a vein once a day for 30 minutes • EKG will be done on Day 1 of cycle 2 only to check your heart
Cycle 3 onwards	• CT scans to determine how your tumor is responding to the treatment will be done every 2 cycles (about every 6 weeks).

Alternative Approaches or Treatments

What other choices do I have if I do not take part in this study?
Talk to your doctor about your choices before you decide if you will take part in this study. Your other choices may include:

- Getting treatment or care for your cancer without being in a study.
- Taking part in another study. However, if you have moderate or severe abnormal liver function, you may not be eligible for most other studies.
- Getting comfort care, also called palliative care. This kind of care helps reduce pain, tiredness, appetite problems, and other problems caused by cancer. It does not treat the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Risks or Discomforts of Taking Part
What side effects or risks can I expect from being in this study?

If you choose to take part in this study, there is a risk that you may:

- Lose time at work or home and spend more time in the hospital or doctor's office than usual
- Be asked sensitive or private questions which you normally do not discuss

The agents used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health. There is also a risk that you could have side effects from the study drug(s)/study approach. Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.

- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

It is important to remember that this is a dose-ranging study, meaning that the dose of belinostat will increase between groups of patients until notable side effects are seen. Because of this, some patients may have severe side effects as the study investigators find the highest dose of belinostat can be given safely to patients with different degrees of liver function. We already know the "safe dose" for patients with normal liver function and will not give you a dose bigger than this. If a dose has too many or certain unacceptable side effects, a lower dose may be recommended as the "safe dose" for future testing in patients with abnormal liver function.

Risks and side effects observed with **belinostat** include:

COMMON, SOME MAY BE SERIOUS In 100 people receiving belinostat, more than 20 and up to 100 may have:
• Diarrhea, nausea, vomiting • Tiredness

OCCASIONAL, SOME MAY BE SERIOUS In 100 people receiving belinostat, from 4 to 20 may have:
• Anemia which may require blood transfusion • Belly pain • Constipation • Dry mouth • Swelling of arms, legs • Fever • Swelling and redness at the site of the medication injection • Infection • Change in the heart rhythm • Bruising, bleeding • Weight loss, loss of appetite • Dehydration • Dizziness, headache • Changes in taste • Shortness of breath • Rash • Flushing

Side Effects of Blood Draw:
Infrequent (occurs in 1 to 10 out of 100 people): persistent pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Birth Control
If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how belinostat would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment and for the entire time you are in the study. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:
- abstinence
- intrauterine device (IUD)
- hormonal (birth control pills, injections, or implants)
- tubal ligation
- vasectomy

Potential Benefits of Taking Part
Are there benefits to taking part in this study?
We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

What are my rights if I take part in this study?
Taking part in this study is your choice. You may choose either to take part or not to take part in this study. If you decide to participate, you may leave the study at any time. No matter what decision you make, there will be no penalty to you, and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution if you are eligible and choose to participate in another trial. We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study. In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

What are the costs of taking part in this study?

The National Cancer Institute will supply the Belinostat at no charge while you take part in this study. The NCI does not cover the cost for getting the Belinostat ready and giving it to you, so

you or your insurance company may have to pay for this. Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the Belinostat to the NCI for some reason. If this would occur, other possible options are:

- You may be able to get the Belinostat from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.

- If there is no Belinostat available at all, no one will be able to get more and the study would close.

If a problem with getting Belinostat occurs, your study doctor will talk to you about these options.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://cancer.gov/clinicaltrials/understanding/insurance-coverage. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

Stopping Therapy
Your doctor may decide to stop your therapy for the following reasons:
- if he/she believes that it is in your best interest
- if your disease gets worse during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you
- if too many patients in the study experience severe side effects

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases cannot be recalled and destroyed.

Will my medical information be kept private?
We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records, including research records, for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people.
- Qualified representatives from the drug company sponsor may also review the medical records.
- Designees from cancer centers participating in this study.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What happens if I am injured because I took part in this study?
It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number]*.

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

Who can answer my questions about the study?
You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).*

[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]

Where can I get more information?
You may call the National Cancer Institute's Cancer Information Service at: 1-800-4-CANCER (1-800-422-6237). You may also visit the NCI Web site at http://cancer.gov/.

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant _____

Date _____

APPENDIX H: REGISTRATION PROCEDURES

I. Registration Policies

A. Registrations for the Liver Dysfunction Trial must be made through the Coordinating Center, at the National Cancer Institute's Center for Cancer Research through the Developmental Therapeutics Clinic. Patients are registered Monday through Friday between the hours of 8:30am through 4:30pm, excluding Federal Holidays. Documentation of IRB approval of this protocol by collaborating institutions must be on file.

B. Following registration, patients should begin protocol treatment within 3 business days. However, beginning therapy within 24 hours of registration is preferable in patients with organ dysfunction.

C. Pre-study laboratory tests and scans must be completed prior to registration, within the time frame specified in the protocol. The eligibility form provided by the NCI, CCR (Appendix J) must be completed and signed by the treating physician. Patients must also sign an informed consent and HIPAA authorization form prior to registration.

D. A patient failing to meet all protocol requirements cannot be registered. If you have any questions regarding eligibility, contact the DTC at (301) 435-4949

II. Slot Reservations

A. If a potential patient has been identified for the Liver Dysfunction trial, the data manager or research nurse must contact the DTC Research Nurse at (301) 435-4949 to verify that a slot is available on a particular dose-level. Please provide the patient's initials, diagnosis, bilirubin, and AST at that time.

1. If a dose level is open, the Research Nurse will reserve the "slot" for a maximum of 14 days (10 business days) to allow sufficient time to determine eligibility. If a patient does not start treatment within this time frame, the slot will be released. Slots will be released on a first come first served basis for all slots other than the normal cohort slots.

a. The data manager or research nurse must follow up the NCI, CCR within 14 days (10 business days) to complete the registration or cancel the reservation.

2. If no dose-level is open (based on the criteria for dose expansion or escalation- as described in the protocol), then the NCI, CCR can indicate the anticipated date of reopening and the slot may be reserved for the patient.

a. The data manager or research nurse must stay in touch with the NCI, CCR and must complete or cancel registration within 24 hours of the planned treatment date. It is preferred that the Coordinating Center is informed of the intended treatment date at least 48 hrs prior.

3. No more than 3 patients may be held on the waiting list for a single liver dysfunction cohort.
    a. If a patient on the waiting list becomes ineligible, then the data manager or research nurse must call or email the Coordinating Center to remove the patient from the list.
4. No slot reservation at the given dose level will be made prior to escalation or expansion until such time as the 3rd patient at that level has been evaluated for toxicity.

III. Registration Procedures

A. Once a patient is eligible, and all the pre-study requirements have been fulfilled, a data manager or research nurse must contact the Coordinating Center's Primary Research Nurse: Nancy Moore RN, phone (240) 760-6045, nancy.moore@nih.gov, fax (301) 451-5625.

B. Fax a copy of the signed informed consent, HIPAA authorization form, eligibility screening worksheet, required pre-study tests (pathology and baseline laboratory reports), and the completed On-Study/Eligibility Form. NCI registration form to (301) 480-7281. Upon receipt of the documents, the Coordinating Center, will confirm completion of the registration process and verify eligibility.

C. All eligible patients will be registered through the NCI Central Registration Office (CRO). The CRO is open from 8:30am to 5:00pm EST Monday through Friday, excluding Federal Holidays. The CRO will notify the Coordinating Center via encrypted e-mail that the protocol Eligibility Checklist has been received and registered.

D. The Coordinating Center will contact the registering data manager or research nurse via email confirming registration. The email confirmation will be available and sent to the participating site within 1 business day. The confirmation of registration form includes patient name, cohort, dose level, NIH medical record number, unique identifier (7 digit number), and an assigned patient ID.

IV. C3D Database Patient ID

A. Upon registration, the CRO will assign a unique 7 digit patient/subject ID number for each patient that will be used to enter data into the C3D database. The number is coded to identify the patient number according to the participating site. The number will appear as 1010001, the first three digits identify the site 101. Subsequent sites will be listed as 102, 103, 104, etc. The last three digits in the series will identify the sites patient number 001.

B. This assigned unique identifier is to be used in the Patient ID field for the CTEP-AERS submission and Theradex Data Reporting.

C. Each site will be listed in the C3D database according to the CTEP assigned code. Each site is assigned a 5 character code composed of an alphabetical site abbreviation and numbers.

V. Assigned Patient ID

A. The CTEP site abbreviation will be utilized along with the last three digits in the unique identifier to reference the patients during the biweekly Organ Dysfunction conference call.

B. The assigned patient ID is an alpha numeric code that will be used to reference the participating site, patient number dysfunction cohort, and dose level.

C. The alphabetical site abbreviation is combined with the last three digits of the unique identifier, cohort letter, and dose level to formulate the assigned Patient ID. Each dysfunction cohort will be referenced alphabetically as Cohort A (Normal), Cohort B (Mild), Cohort C (Moderate), Cohort D (Severe). The assigned ID will appear as NCI-001-A-1.

D. The assigned ID will also be used as the Patient ID to code the pharmacokinetic samples.

APPENDIX I: Organ Dysfunction Conference Call Policies

I. Biweekly Conference Call Policies

a. A master liver dysfunction slot reservation excel spreadsheet will be maintained and distributed biweekly to the participating site 24 hours prior to the conference call.
b. Each participating site is required to have at least one representative participating in the conference call.
c. Patients will be referenced using the assigned Patient ID.
d. Sites are required to provide an update on each active patient.

II. Protocol Enrollment Log

a. A patient enrollment log template word version will be distributed to each participating site.
b. Data managers or research nurses should maintain and update the log
c. The updated log should be sent via email to the Coordinating Center by 2pm EST the Thursday prior to the Friday Conference Call.

APPENDIX J: Forms

Eligibility/Pre-Registration Worksheet
CTEP #8846, NCI #11-C-0060

A Phase I Pharmacokinetic Study of Belinostat for Solid Tumors and Lymphomas in Patients with Varying Degrees of Hepatic Dysfunction

Coordinating Center: NCI
Bethesda, MD 20892
Primary Contact: Nancy Moore, RN
Tel: (240) 760-6045
Fax: (301) 451-5625
nancy.moore@nih.gov

Principal Investigator:
Naoko Takebe, MD, PhD
National Cancer Institute
Tel: (240) 781-3398
takeben@mail.nih.gov

Patient's Name: (FML)	Institution:	
Medical Record Number:	Investigator:	
Patient's Date of Birth:	Treating Physician:	
Sex: _____Male _____Female	Date Informed Consent Signed:	
IRB approval valid until (date)		
Race: _____ Black _____ Caucasian _____ Asian _____ American Indian _____ Native Hawaiian/Pacific _____ Other: _____	Ethnicity: ____ Hispanic ____ Non-Hispanic ____ Other: _____	Projected start date of treatment:

INCLUSION CRITERIA: A **NO** response will make the subject **INELIGIBLE**.

Yes	No	N/A	INCLUSION CRITERIA
			Does the patient (except those with hepatocellular carcinoma) have histologically or cytologically confirmed solid tumor or lymphoma that is metastatic, unresectable, progressive, or recurrent, and for which standard curative or palliative measures do not exist or are no longer effective? Patients with hepatocellular carcinoma do not require biopsy confirmation. If the patient has hepatocellular carcinoma, does the patient have a liver mass with raised α-fetoprotein level (≥500 ng/mL), consistent radiographic changes, and serology and viral DNA/RNA measurements consistent with chronic hepatitis (see Section 3.1.9) AND have disease that has failed standard therapy?
			Is it correct that the patent has had no radiation, major surgery, chemotherapy or biologic therapy within 4 weeks prior to entering the study (6 weeks for nitroureas or mitomycin C); ≥ 2weeks since any prior administration of study drug in an exploratory IND/Phase 0 study. Has the patient recovered to at least eligibility levels due to adverse events and/or toxicity of prior chemotherapy or biologic therapy?
			Is the patient's age ≥ 18 years? Because no dosing or adverse event data are currently available on the use of Belinostat in patients <18 years of age, children are excluded from this study but will be eligible for future pediatric Phase 1 single-agent trials.
			Is the patient's ECOG performance status ≤ 2 and Karnofsky ≥60%, (Appendix B)? **Status _____**
			Is the patient's life expectancy greater than 3 months?
			Does the patient have acceptable renal and marrow function as defined below? Date: _____ **Leukocytes ≥ 3,000/mcL** _____ **Absolute Neutrophil Count (ANC) ≥ 1,5000/mcL** _____ **Platelets ≥ 100,000/mcL** _____ **Serum Creatinine** _____ ULN _____ **(within normal institutional limits)** **OR** **Creatinine Clearance** **≥ 60 mL/min for patients with creatinine levels above institutional normal, as determined by measured 24-hour creatinine clearance** Baseline evaluations should be conducted within 7 days of the treatment start date. Patients with abnormal liver function will be eligible and will be grouped according to the criteria described in Section 5.1. No distinction will be

Yes	No	N/A	INCLUSION CRITERIA
			made between liver dysfunction due to metastases and liver dysfunction due to other causes. Liver function tests should be repeated with 24 hours prior to starting treatment on study
			Patients with biliary obstruction for which a stent has been placed are eligible, provided the stent has been in place for at least 10 days prior to the first dose of belinostat and the liver function has stabilized. Two measurements at least 2 days apart that put the patient in the same hepatic dysfunction stratum will be accepted as evidence of stable hepatic function. There should be no evidence of biliary sepsis. Does the patient either not have a stent, or, if a stent is in place, has it been in place for over 10 days, AND has the liver function shown stability (placing patient into same cohort with measurements at least 2 days apart)?
			If patient has hepatitis B, are HepBsAg, HepBcAb, HepBsAb, and HepBeAb consistent with chronic disease as measured within 3 months of starting on study?
			If patient has hepatitis B, has COBAS TaqMan been checked within 1 month of starting on study?
			If patient has hepatitis C, has anti-HCV been checked within 3 months of starting on study?
			If patient has hepatitis C, has HCV-RNA been checked within 1 month of starting on study?
			Patient with gliomas or brain metastases who require corticosteroids or anticonvulsants must be on a stable dose of corticosteroids and seizure free for 1 month prior to enrollment. Patients with known brain metastases should have had brain irradiation (whole brain or gamma knife) more than 4 weeks before starting the protocol. Note that patients should have had their steroids tapered to low dose (i.e., 1.5 mg of dexamethasone/day). Does the patient either **not** have gliomas or brain metastases, or if the patient does, have they met the above criteria?
			Is the patient able to understand and willing to sign a written informed consent document?
			The effects of belinostat on the developing human fetus are unknown. For this reason and because HDAC inhibitors 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. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Does the patient agree to use contraception for the duration of study participation?

EXCLUSION CRITERIA: A **YES** response will make the patient **INELIGIBLE** for the study.

Yes	No	N/A	EXCLUSION CRITERIA
			Is the patient receiving any other investigational agents?
			Has the patient previously been treated with Belinostat?
			Does the patient have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to belinostat, including hydroxamate compounds or arginine?
			Has the patient taken valproic acid, another HDAC inhibitor, within 2 weeks prior to enrollment?
			Does the patient have uncontrolled intercurrent illness including, but not limited to ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements?
			Is the patient pregnant or breastfeeding? Pregnant women are excluded from this study because belinostat is an HDAC inhibitor with the potential for teratogenic or abortifacient effects.
			Does the patient have active hemolysis? Patients with active hemolysis should be excluded.
			Is the patient on antiretroviral therapy? HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for PK interactions with belinostat. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.
			For patients with hepatitis B or C, does the patient require interferon treatment or has the patient received interferon within the past 4 weeks? Patients must be stable without having received interferon in at least 4 weeks.
			Does the patient have significant cardiovascular disease (New York Heart Association Class III or IV cardiac disease), symptomatic congestive heart failure, myocardial infarction within the past 6 months, unstable angina, unstable arrhythmia or a need for anti-arrhythmic therapy (use of frequency adjusting medication for atrial fibrillation is allowed, if stable medication for at least last month prior to initiation of belinostat treatment and medication not listed as causing Torsades de Points), evidence of acute ischemia or ECG, marked baseline prolongation of QT/QTc interval, e.g., repeated demonstration of a QTC interval > 450 msec*; Long QT Syndrome? Or does the patient require a drug known to prolong the QT interval and/or cause Torsades de Pointes (Table 1, Appendix C) or have taken such a drug within 2 weeks of study entry? (Note: Drugs that may be associated with Torsades de Pointes but lack substantial evidence [Table 2, Appendix C] will be allowed at the discretion of the PI, although it is preferable to substitute an alternate medication.)

PRE-STUDY EVALUATIONS

Laboratory evaluations are to be conducted within 1 week prior to the start of the protocol therapy unless otherwise indicated. Scans and x-rays must be performed within 28 days prior to the start of therapy.

Pre-Study Evaluations:	Completion Date
History and Physical Exam: (prior to study drug administration) (including height, weight, vital signs, and Performance Status)	
Baseline Imaging Studies: (CT Scan of the Chest/Abd/pelvis within 28 days prior to study drug administration)	
Laboratory Evaluation: (within 1 week prior to study drug administration) Hematological Profile: CBC with differential and Platelet Count Coagulation Studies: PT*/INR/aPTT* is required to be checked at baseline Biochemical Profile: Electrolytes, BUN, creatinine, glucose, AST (SGOT), ALT (SGPT), bilirubin, calcium, phosphorous, albumin, magnesium, alkaline phosphatase. *=as clinically indicated	
Serum Pregnancy Test: (within 1 week prior to study drug administration) Participants of childbearing age and anatomic ability.	
EKG (within 1 week prior to study drug administration)	
Child-Pugh Classification score (Appendix M). Please submit with enrollment package.	
Histologic Confirmation: A block or stained slides of primary tissue from the time of diagnosis will be required from each participant to confirm diagnosis. Tissue blocks from a known recurrence will be accepted if original tumor samples are unavailable.	

Laboratory evaluation for patients with hepatocellular carcinoma secondary to hepatitis B or C: For patients with hepatitis B HepBsAg, HepBcAb, HepBsAb, and HepBeAb; results may be from within 3 months before starting on study. COBAS TaqMan; results must be from within 1 month before starting on study. For patients with hepatitis C anti-HCV; results may be from within 3 months before starting on study. HCV-RNA; results must be from within 1 month before starting on study.	

DESCRIPTIVE FACTORS:

Primary: _____ Histology: _____

Height _____ cm Weight _____kg BSA _____

PRIOR THERAPY (Please specify date, procedure, agent, dose, and response)

Treatment Type	Agent	Treatment Start Date	Treatment End Date	Response
Surgery/Biopsy:				
Chemotherapy:				
Radiotherapy:				

Hormonal Therapy:				
Immunotherapy:				

LIVER DYSFUNCTION GROUPS

Patients entering the study are stratified into four dysfunction groups [(Cohort 1) Normal, (Cohort 2) Mild, (Cohort 3) Moderate, (Cohort 4) Severe] according to their hepatic function as outlined in the following table:

Liver Dysfunction Cohorts	Cohort 1 Normal	Cohort 2 Mild	Cohort 3 Moderate	Cohort 4 Severe
Total Bilirubin	≤ ULN	>ULN but ≤ 1.5 X ULN	>1.5 X ULN to ≤ 3 X ULN	> 3 X ULN but ≤ 10 X ULN
AST (SGOT)	≤ ULN	AST > ULN	Any AST	Any AST

HEPATIC FUNCTION

Total Bilirubin:

Normal Cohort 1: ≤ ULN ☐

Mild Cohort 2: > ULN but ≤ 1.5 X ULN ☐

Moderate Cohort 3: >1.5 X ULN to ≤ 3 X ULN ☐

Severe Cohort 4: > 3 X ULN but ≤ 10 X ULN ☐

AST (SGOT):

Normal Cohort 1: ≤ ULN ☐

Mild Cohort 2: > ULN ☐

Moderate Cohort 3: Any AST ☐

Severe Cohort 4: Any AST ☐

Date Measured _____

(Second Measurement – for patients with a biliary stent)

Patients should have biliary stent placed at least 10 days prior to the start of treatment. Provide the placement date in the table, if placed within 10 days of treatment.

Biliary Stent Present	Yes	No	Biliary Stent Placement Date	Second Lab Measurement Date

Liver Dysfunction Group

Normal Cohort 1: ☐

Mild Cohort 2: ☐

Moderate Cohort 3: ☐

Severe Cohort 4: ☐

Printed Name of Physician: _____ Date: _____
Physician Signature: _____

Date Registered with NCI _____
Spoke with: _____
Study ID: _____
Eligibility Completed Complete By: _____
Assigned CRA/ Data Manager: _____

The NCI will send a confirmation of registration within 24 hours.

Appendix K: Off Study/Death Notification Form

Complete form and e-mail to the Coordinating Center Research Nurse
nancy.moore@nih.gov

Patient Information:

First Name: ☐

Middle Initial: ☐

Last Name: ☐

ID Number: ☐

Protocol # (CC# Preferred): ☐

Off Study Date: ☐ (MM/DD/YY)

Death Date: ☐ (MM/DD/YY)

Choose one of the following Off Study Reasons:

- ☐ **C:** Completed Study
- ☐ **L:** Lost to Follow Up
- ☐ **R:** Refused Further Treatment
- ☐ **T:** Toxicity
- ☐ **D:** Death
- ☐ **P:** Progressive Disease
- ☐ **O:** Other ☐

Registrar:
Participating Site: _____
Name: _____ Date: _____

Appendix L: Study Diary
Phase I Belinostat for Solid Tumors and Lymphomas in Patients with Varying Degrees of Hepatic Dysfunction

Patient Name: _____ Cycle _____ Week _____
Cohort: _____

Date	Note any side effects	List any medications taken and the reason why (prescription & non-prescription) **Do not list your daily meds**
Monday **Date:**		
Tuesday **Date:**		
Wednesday **Date:**		
Thursday **Date:**		
Friday **Date:**		
Saturday **Date:**		
Sunday **Date:**		

Patient Signature: _____ Date: _____

APPENDIX M: Child-Pugh Classification (CPC) of Liver Dysfunction

CPC score is calculated from the sum of the points for each CPC criteria:

CPC Classification	Level of dysfunction	Score
A	Mild	5-6
B	Moderate	7-9
C	Severe	≥10

	Points		
CPC Criteria	**1**	**2**	**3**
Encephalopathy grade (see table below)	0	1 or 2	3 or 4
Ascites	Absent	Asymptomatic	Requiring intervention
Serum bilirubin, mg/dL	<2	2 to 3	>3
Serum albumin, g/dL	>3.5	2.8 to 3.5	<2.8
Prothrombin time, sec prolonged	<4	4 to 6	>6

Encephalopathy Grade	Definition (EEG required for Gr. 2,3,4)
0	Normal consciousness, personality, neurological exam
1	Restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting
2	Lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves on EEG
3	Somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves on EEG
4	Unrousable coma, no personality/behavior, decerebrate, slow 2-3 cps delta activity on EEG

CPC should be calculated at baseline as part of the eligibility assessment.