Phase I Study of Panobinostat Plus ICE Chemotherapy Followed by A Randomized Phase-II Study of ICE compared with Panobinostat Plus ICE For Patients With Relapsed and refractory Classical Hodgkin Lymphoma

1.0 OBJECTIVES:

1.1 Primary objective:

- Phase-I: To determine the maximal tolerated dose (MTD) of panobinostat + ICE combination
- Randomized Phase-II: To estimate the complete response (CR) rate in patients with relapsed and refractory classical HL receiving ICE versus PANOBINOSTAT (LBH589) plus ICE therapy

1.2 Secondary Objectives:

- To assess the safety and tolerability of the novel combination of PANOBINOSTAT (LBH589) plus ICE versus ICE in patients with relapsed and refractory HL
- To estimate the overall response rate (CR + PR)
- To estimate the success rate of stem cell collection in patients eligible for stem cell transplant
- To estimate the percentage of patients who subsequently undergo autologous stem cell transplantation (ASCT)
- To estimate the event free survival (EFS) at 1 year after randomization
- To determine pretreatment expression level of HDAC1, HDAC2, and pSTAT3 and pSTAT6 by IHC and correlate the results with treatment response

2.1 BACKGROUND AND RATIONALE

2.2 **Hodgkin lymphoma (HL):** This year, it is estimated that 7200 patients will be diagnosed with Hodgkin lymphoma (HL) and 54,000 will be diagnosed with NHL.[1] Although HL is one of the most curable human cancers, the management of refractory and relapsed disease remains challenging.[2,3] With the exception of high dose therapy followed by stem cell transplant, there is no curative treatment for patients with relapsed disease. New innovative treatment strategies are clearly needed.

2.2 Rational for using HDACi in HL: Molecular analysis demonstrated that the malignant Hodgkin and Reed-Sternberg (HRS) cells of Hodgkin lymphoma (HL) are of B-cell origin. However, HRS cells infrequently express B-cell antigens. This loss of B-cell phenotype has been reported to be epigenetically regulated and is thought to enable HRS cells to evade immunosurveillance. For example, gene expression profiles of HRS cells revealed decreased mRNA levels for nearly all B-cell lineage-specific genes.[4] The decrease in mRNA expression was associated with downregulation of protein expression in primary HL cases, as determined by immunohistochemistry, including CD20, CD19, Syk, Lck, Blk, Oct-2, and B-cell receptor.[4] Furthermore, microdissected primary HRS cells and HL cell lines are downregulated in HL. Furthermore, data from our laboratory demonstrated that HDAC inhibitors have direct antiproliferative effects on HL cell lines.[5] This effect was associated with induction of p21 and TRAIL death receptor (TRAIL-R) 1 and TRAIL-R2, and downregulation of STAT6 expression, in addition to cleavage of caspase 3 and increase in annexin-V membrane binding.

We and others recently demonstrated promising clinical activity of a variety of HDACi therapy in heavily pre-treated patients with relapsed HL, including MGCD0103 and panobinostat.[6] MGCD-0103, is a novel oral nonhydroxymate benzamide-based HDAC inhibitor that selectively inhibits HDAC 1 and 2 (and to a lesser extent, 3 and 11) isoforms.[7] The IC_{50} for inhibiting recombinant HDAC1 activity is 0.082 μM compared with >30 μM for HDAC6.[8,9] The safety and efficacy of MGCD0103 was recently evaluated in a phase-II study in patients with relapsed and refractory HL.[6] In the absence of disease progression or prohibitive toxicity, patients were allowed to continue therapy for a maximum of 12 months. Initially, 20 patients were treated with 110 mg orally given three times per week. Seven (35%)

patients achieved partial and complete remissions. However, treatment was discontinued after a median of 4.5 months due to grade 3 or 4 toxicity. Subsequently, the study was revised to allow a lower starting dose of 85 mg at the same schedule. Three of the 10 (30%) patients enrolled on the reduced dose achieved partial remissions. Furthermore, grade 3 and 4 toxicity was reduced to 20%. Overall, 80% of the 30 evaluable patients had some decrease in their tumor measurements. Although none of the patients developed significant EKG abnormalities, two patients developed pericardial effusions requiring discontinuation of therapy. In a second trial, panobinostat, a potent pan-DAC inhibitor, was recently evaluated in a phase-I study in patients with hematologic malignancies that also included patients with HL.[10] Five of 13 (38%) patients achieved partial remissions. The most common side effects were fatigue, nausea, and diarrhea. Furthermore, 38% of the patients developed grade 4 thrombocytopenia. However, no clinically significant cardiac toxicity was reported. Based on this promising clinical activity, a large international phase-II study of panobinostat in relapsed HL is now enrolling patients to confirm these results. Finally, the Southwest Oncology Group (SWOG) conducted a phase-II study of vorinostat in patients with relapsed HL.[11] Twenty-five patients were treated with 200 mg vorinostat given orally twice per day for 14 days every 21 day-cycle. Unlike MGCD0103 and panobinostat, vorinostat produced modest clinical activity, as only one patient (4%) achieved a partial remission.

Collectively, these data suggest that HDACi may have a potential therapeutic value in patients with relapsed HL.

We and others recently demonstrated a promising clinical activity of MGCD0103, a class-I selective HDACi, in heavily pre-treated patients with relapsed HL.[6] Patients with relapsed or refractory HL are treated with 110 mg orally on a Monday-Wednesday-Friday schedule. After 2 months of therapy, patients are evaluated for tumor response. If no disease progression or prohibitive toxicity is observed, patients are allowed to continue therapy for a maximum of 12 months. Twenty-one patients were treated with the 110 mg starting dose, of whom 38% achieved partial and complete remissions. However, grade 3/4 toxicity were observed in 39% of the patients, leading to early discontinuation of therapy (median PFS = 4.5 months). Subsequently, the study was revised to allow a lower starting dose of 85 mg at the same schedule. Ten patients are already enrolled on the reduced dose, of whom five patients completed 2 months of therapy and are evaluable for treatment response. One patient (20%) achieved a partial response, and grade 3/4 toxicity was reduced to 20%. Overall, 88% of the 26 patients had some decrease in their tumor measurements and only 3 patients had disease growth while on therapy. To date, no significant hematologic or cardiac toxicities have been observed. Thus, the encouraging clinical activity coupled with the reasonable safety profile (especially using the reduced starting dose of 85 mg), supports further developing this therapy for patients with relapsed HL.

In an ongoing Phase I trial, panobinostat is administered orally, once/day, on Mon/Wed/Fri (MWF), every week (Arm 1) or every other week (Arm 2), in 28-day cycles, to adult patients (pts) with advanced hematologic malignancies including HL. Preliminary results from this ongoing phase-I study demonstrated a 30% response rate in patients with relapsed HL. The most common side effects were fatigue, nausea, diarrhea, and thrombocytopenia.

Collectively, these data suggest that HDACi may have a potential therapeutic value in patients with relapsed HL.

2.3 Experience with Ifosphamide, Carboplatin, and Etoposide (ICE) regimen in patients with relapsed HL: ICE has been previously studied in patients with refractory and relapsed HL. In 65 transplantation-eligible patients were treated with the ICE regimen as follows: Ifosphamide 5 gm/m2 mixed with an equal dose of MESNA administered by continuous infusion for 24 hours beginning on day 2, Carboplatin dosed to an area under the curve (AUC) of 5 (the maximum dose was 800 mg) beginning on day 2, and Etoposide 100 mg/m2 per day on days 1, 2 and 3. All patients received GCSF support on days 5-12. No dose reductions were allowed, but treatment was delayed until the absolute

neutrophil count (ANC) was > 1000/µL, and the platelet count was > 50,000/µL. PBPCs were mobilized after the second cycle of ICE chemotherapy using G-CSF (10 µg/kg per day) beginning on day 5 and continuing until the completion of leukapheresis). Leukapheresis was initiated when the white blood cell count was greater than 5000/µL. For the first 30 patients leukapheresis was performed daily until more than 2×10^6 $CD34^+$ cells/kg were collected; a back-up bone marrow harvest was also taken for each patient. For the remaining 35 patients, bone marrow harvest was performed only if apheresis yielded less than 2×10^6 $CD34^+$ cells/kg. Each patient underwent a maximum of 5 apheresis procedures. The mobilization procedure was considered to have failed if less than 2×10^6 $CD34^+$ cells/kg were collected in a patient after 5 apheresis procedures; bone marrow and PBPCs were then reinfused for ASCT. The study was conducted between 1994 and 1998 before the incorporation of PET scanning in response assessment. Furthermore, the response criteria that was used and the definition of complete remission (CR) was not clearly stated. Finally, 41 of 57 patients with chemosensitive disease received involved field or multiple cite radiation therapy, further blurring the CR rate achieved by ICE. Results from that study is shown in Table-1 below:

Table-1: Summary results of ICE therapy in patients with relapsed HL

Regimen	N	CR (%)	PR (%)	CR + PR	Ref
ICE	65	17 (26%)	38 (58%)	84%	[12]

2.4 Rationale for combining PANOBINOSTAT (LBH589) with ICE: Based on several published reports demonstrating synergy between chemotherapy and a variety of HDACis in vitro, we propose to combine PANOBINOSTAT (LBH589) with standard ICE chemotherapy regimen. The primary goal of this approach is to increase the CR rate prior to autologous stem cell transplant (ASCT).

2.5 Rationale for adjusting dosing schedule of Panobinostat (LBH589) with ICE: Previously published data showed 26% of patients had delay in receiving ICE every 2 cycles due to thrombocytopenia. After enrolling 21 patients on this current protocol administering panobinostat 3x/week continuously unless required to hold due to AE, all patients were unable to receive ICE as planned every 2 weeks and were delayed a week, with the primary cause for delay due to thrombocytopenia. Therefore in order to compare efficacy of panobinostat+ICE in this trial to that reported in previous trial, the dosing schedule of panobinostat will be adjusted and an additional 10 patients enrolled (Dosing Schedule B).
Based on findings of this expanded cohort, both schedules will be considered for additional cohorts and/or phase II portion of the trial.

3.0 DRUG INFORMATION

Anticancer activity of DAC inhibitors
Alterations in chromosome structure play critical roles in the control of gene transcription. These epigenetic alterations include modification of histones and others proteins by acetylation and/or phosphorylation. Normally, these modifications are balanced finely and are highly reversible in normal tissues, but they may be imbalanced and heritable in tumor cells. DAC inhibitors increase histone acetylation, thereby modulating the expression of a subset of genes in a coordinated fashion. Several tumors suppressor genes associated with the malignant phenotype are repressed by epigenetic mechanisms in sporadic cancers. Thus therapy with DAC inhibitors may alter tumor phenotype and inhibit growth in such tumors.
Multiple hallmarks of cancer are regulated by acetylation/deacetylation:

- DAC inhibition targets both histone and nonhistone proteins. Targeting the acetylation status of nonhistone, tumor-associated proteins that mediate proliferation may be the underlying antitumor mechanism of DAC inhibitors (Marks 2001).

- Nonhistone proteins regulated by acetylation include α-tubulin, p53, HIF-1α, and HSP90. These proteins are substrates of DACs. (Glozak 2005).
- The ability of a single agent to target multiple molecular features of tumor cells may result in good efficacy against a range of different tumor types.
- HSP90 is involved in protein stability and degradation; the inhibition of HSP90 affects protein turnover in diseases such as multiple myeloma and B-cell malignancies (Aoyagi 2005)
- Acetylated HIF-1α is degraded and can no longer act as a tumor growth factor. Class II DAC inhibitors target histone deacetylase (HDAC or DAC) 6, resulting in increased acetylation of HIF-1α and decreased vascular endothelial growth factor (VEGF), thereby inhibiting angiogenesis (Diaz-Gonzalez 2005).
- Both acetylation and ubiquitylation often occur on the same lysine residue, but these processes cannot occur simultaneously. Acetylation allows for increased stability, and ubiquitylation leads to protein degradation. Therefore, DACs decrease the half-life of a protein by exposing the lysine residue for ubiquitylation (Walsh 2005).

3.1
PANOBINOSTAT (LBH589). Panobinostat (LBH589) is a deacetylase inhibitor (DACi) belonging to a structurally novel cinnamic hydroxamic acid class of compounds. It is a potent class I/II pan-DAC inhibitor (pan-DACi) that has shown anti-tumor activity in pre-clinical models and cancer patients. Deacetylases (DAC) target lysine groups on chromatin and transcription factors and various non-histone proteins such as p53, tubulin, HSP90 and Rb. Panobinostat is formulated as an oral capsule and a solution for intravenous (i.v.) injection. Both the oral and i.v. formulations are currently being investigated in ongoing Phase I and Phase II studies in advanced solid tumors and hematological malignancies.

Inhibition of DAC provides a novel approach for cancer treatment. Histones are part of the core proteins of nucleosomes, and acetylation and deacetylation of these proteins play a role in the regulation of gene expression. Highly charged deacetylated histones bind tightly to the phosphate backbone of DNA, inhibiting transcription, presumably, by limiting access of transcription factors and RNA polymerases to DNA. Acetylation neutralizes the charge of histones and generates a more open DNA conformation. This conformation allows transcription factors and associated transcription apparatus access to the DNA, promoting expression of the corresponding genes. The opposing activities of two groups of enzymes, histone acetyltransferase (HAT) and DAC control the amount of acetylation. In normal cells a balance exists between HAT and DAC activity that leads to cell specific patterns of gene expression. Perturbation of the balance produces changes in gene expression.

Several lines of evidence suggest that aberrant recruitment of DAC and the resulting modification of chromatin structure may play a role in changing the gene expression seen in transformed cells. For example, silencing of tumor suppressor genes at the level of chromatin is common in human tumors (Herman 1994, Pratt 1994, Szyf 1994, Herman 1995, Merlo 1995, Herman 1996, Herman 1998, Cameron 1999) and DAC complexes have been shown to be crucial to the activity of the AML-specific fusion proteins PLZF-RAR-α, PML-RAR-α, and AML1/ETO (Gelmetti 1998, Grignani 1998, Lin 1998, Redner 1999). DAC inhibitors (DACi) have been shown to induce differentiation, cell cycle arrest or apoptosis in cultured leukemia cells, and to inhibit the growth of tumors in animal models (Yoshida 1987, Yoshida 1988, Itazaki 1990, Yoshida 1990, Sugita 1992, Yoshida 1992, Medina 1997). In addition, DACi have been shown to induce expression of p21, a key mediator of cell cycle arrest in G1 phase and cellular differentiation (Biggs 1996, Nakano 1997, Sowa 1997, Sambucetti 1999).

Tumor growth inhibition and apoptosis in response to DACi treatment may also be mediated through changes in acetylation of non-histone proteins (e.g., HSP90, p53, HIF-1α, α-tubulin). For example, the chaperone protein HSP90 has been shown to be acetylated in cells treated with DACi Many proteins

that require HSP90 association are critical to cancer cell growth, including ErbB1, ErbB2, AKT, Raf, KDR, and BCR-ABL. Acetylation of HSP90 in cells treated with DACi inhibits the chaperone function of HSP90, leading to degradation of the client proteins and eventual cell death.

The potential clinical utility of the use of DACi in cancer therapy was first suggested by the activity of the DACi, sodium phenylbutyrate, against acute promyelocytic leukemia (APL). An adolescent female patient with relapsed APL, who no longer responded to all trans-retinoic acid (ATRA) alone, achieved a complete clinical remission after treatment with a combination of ATRA and the DACi sodium phenylbutyrate (Warrell 1998). Recent evidence suggests that there is activity in a variety of solid and hematological tumors with Vorinostat (Zolinza™), an orally administered, structurally-related DACi. Vorinostat has been reported to have single-agent activity in cutaneous T-cell lymphoma (CTCL), diffuse large cell lymphoma, and head and neck cancer (Heaney 2003 and Kelly 2003). Similar activity has been reported in clinical studies with other DACi, including i.v. romidepsin (Kim 2007). Vorinostat was approved by the FDA for the treatment of cutaneous manifestations of cutaneous T-cell lymphoma for patients who have progressive, persistent or recurrent disease on or following two systemic therapies in October 2006 (Mann 2007).

Overview of clinical experience

In clinical studies, both oral and i.v. formulations of panobinostat are being explored for further development. As of 31st December 2008, twenty-two clinical studies, including clinical pharmacology, phase I and/or phase II, have either been completed or are ongoing. A total of 789 patients were enrolled, received at least one dose of panobinostat, and for whom safety data are available. These patients constitute the safety population . Most adverse events have been grade 1 or grade 2. The most common adverse events seen in the human studies concern the gastrointestinal tract (nausea, diarrhea) and the hematopoietic system (thrombocytopenia and neutropenia). Additional common toxicities have included fatigue and vomiting. With the exception of thrombocytopenia, grade 3 and 4 adverse events were uncommon. The occurrence of thrombocytopenia appears to be related to the underlying disease (incidence is higher in patients with malignancies that involved the bone marrow e.g., acute myeloid leukemia, chronic myeloid leukemia, multiple myeloma, myelodysplastic syndrome, etc.). The most common ECG findings adjudicated by central review included post-baseline increase in frequency of sinus tachycardia, T-waves changes (flat, biphasic, inverted), as well as depressed ST segment findings. The most frequently encountered laboratory abnormalities were thrombocytopenia, neutropenia, some degree of anemia and fluctuations in electrolytes, that might not be clinically relevant Thyroid function, as monitored by the measurement of TSH and free T4, did not reveal overt hyper- or hypo- thyroidism, with fluctuations in TSH values being within normal limits. Since the dosing in this study will follow the three-times-per-week schedule, Table 1-1 below, provides a summary of adverse events that occurred in >15% of the patients at any dose. Table 0-1 All grade adverse events regardless of causality in patients receiving oral panobinostat three-times per week in hematologic malignancies

Primary System Organ Class PREFERRED TERM	20 mg[a] N = 103 n	30 mg[b] N = 9 n	40 mg[c] N = 14 n	60 mg[d] N = 32 n
Any primary system organ class	**102(99.0)**	**9(100.0)**	**14(100.0)**	**29(90.6)**
Blood and lymphatic system disorders	**70(68.0)**	**6(66.7)**	**12(85.7)**	**26(81.3)**
Anemia	32(31.1)	2(22.2)	2(14.3)	9(28.1)
Febrile neutropenia	9(8.7)	0(0.0)	4(28.6)	12(37.5)
Neutropenia	20(19.4)	3(33.3)	4(28.6)	7(21.9)
Thrombocytopenia	37(35.9)	5(55.6)	7(50.0)	16(50.0)
Cardiac disorders	**12(11.7)**	**2(22.2)**	**5(35.7)**	**7(21.9)**

Primary System Organ Class **PREFERRED TERM**	**20 mg[a]** **N = 103** **n**	**30 mg[b]** **N = 9** **n**	**40 mg[c]** **N = 14** **n**	**60 mg[d]** **N = 32** **n**
Tachycardia	5(4.9)	2(22.2)	1(7.1)	5(15.6)
Ear and labyrinth disorders	**3(2.9)**	**1(11.1)**	**2(14.3)**	**5(15.6)**
Vertigo	1(1.0)	1(11.1)	2(14.3)	4(12.5)
Gastrointestinal disorders	**69(67.0)**	**9(100.0)**	**12(85.7)**	**27(84.4)**
Abdominal pain	7(6.8)	3(33.3)	2(14.3)	9(28.1)
Constipation	13(12.6)	1(11.1)	1(7.1)	3(9.4)
Diarrhea	38(36.9)	4(44.4)	6(42.9)	25(78.1)
Dry mouth	2(1.9)	1(11.1)	4(28.6)	4(12.5)
Nausea	42(40.8)	5(55.6)	12(85.7)	16(50.0)
Vomiting	27(26.2)	2(22.2)	10(71.4)	12(37.5)
General disorders and administration site conditions	**71(68.9)**	**8(88.9)**	**14(100.0)**	**24(75.0)**
Chest pain	1(1.0)	0(0.0)	1(7.1)	4(12.5)
Chills	5(4.9)	1(11.1)	4(28.6)	7(21.9)
Fatigue	41(39.8)	5(55.6)	12(85.7)	18(56.3)
Oedema peripheral	20(19.4)	1(11.1)	4(28.6)	7(21.9)
Pyrexia	28(27.2)	4(44.4)	4(28.6)	8(25.0)
Investigations	**38(36.9)**	**5(55.6)**	**7(50.0)**	**15(46.9)**
Blood creatinine increased	10(9.7)	1(11.1)	2(14.3)	5(15.6)
C-reactive protein increased	1(1.0)	0(0.0)	0(0.0)	4(12.5)
Metabolism and nutrition disorders	**53(51.5)**	**6(66.7)**	**10(71.4)**	**25(78.1)**
Anorexia	20(19.4)	4(44.4)	8(57.1)	19(59.4)
Dehydration	2(1.9)	0(0.0)	2(14.3)	4(12.5)
Hypocalcaemia	7(6.8)	1(11.1)	2(14.3)	8(25.0)
Hypokalemia	16(15.5)	5(55.6)	2(14.3)	13(40.6)
Hypophosphataemia	6(5.8)	0(0.0)	0(0.0)	5(15.6)
Musculoskeletal and connective tissue disorders	**40(38.8)**	**2(22.2)**	**9(64.3)**	**10(31.3)**
Back pain	21(20.4)	0(0.0)	2(14.3)	5(15.6)
Nervous system disorders	**40(38.8)**	**4(44.4)**	**10(71.4)**	**18(56.3)**
Dysgeusia	5(4.9)	3(33.3)	4(28.6)	11(34.4)
Headache	14(13.6)	1(11.1)	4(28.6)	8(25.0)
Psychiatric disorders	**13(12.6)**	**3(33.3)**	**6(42.9)**	**8(25.0)**
Insomnia	0(0.0)	1(11.1)	0(0.0)	4(12.5)
Respiratory, thoracic and mediastinal disorders	**39(37.9)**	**4(44.4)**	**10(71.4)**	**15(46.9)**
Cough	8(7.8)	2(22.2)	6(42.9)	8(25.0)

Primary System Organ Class **PREFERRED TERM**	**20 mg[a]** **N = 103** **n**	**30 mg[b]** **N = 9** **n**	**40 mg[c]** **N = 14** **n**	**60 mg[d]** **N = 32** **n**
Dyspnea	19(18.4)	2(22.2)	4(28.6)	6(18.8)
Epistaxis	8(7.8)	0(0.0)	2(14.3)	7(21.9)
Skin and subcutaneous tissue disorders	**24(23.3)**	**4(44.4)**	**6(42.9)**	**12(37.5)**
Petechiae	5(4.9)	0(0.0)	1(7.1)	4(12.5)
Rash	7(6.8)	0(0.0)	2(14.3)	4(12.5)
Vascular disorders	**16(15.5)**	**3(33.3)**	**3(21.4)**	**10(31.3)**
Haematoma	3(2.9)	0(0.0)	2(14.3)	4(12.5)
Hypotension	4(3.9)	1(11.1)	0(0.0)	5(15.6)

[a] Includes patients from [B2102] (group X, group Y, MM only), [B2202], [B2203], and[B2211]; events occurring in ≥10% of patients
[b, & c] Includes patients from [B2102] (group X, group Y, MM only); events occurring in ≥50% of patients
[d] Includes patients from [B2102] (group X, group Y, MM only); events occurring in ≥10% of patients
A patient with multiple occurrences of an AE within one SOC is counted only once in the AE category

Table 1-1 lists adverse events, regardless of causality or grade, reported in patients treated with panobinostat for hematological malignancies. As the number of patients for each dose differs, the following rules apply to which events are listed: in doses where the n is ≥25 patients, events occurring at a rate ≥10% of patients are listed; in doses where the n is <25, events occurring at a rate ≥50% of patients are listed. If the frequency of the event matches the criteria in one dose category, the event is shown for all doses. AEs have been reported for 154 patients (97.5%) within the dataset. The most commonly reported adverse events across doses were fatigue reported for 76 patients (48.1%), nausea for 75 patients (47.5%), and diarrhea for 73 patients (46.2%). There were not significant differences between the groups; a subanalysis between populations and prior medications was not conducted. Within the 40 mg dose group, vomiting was reported at a higher rate than in the 20, 30, and 60 mg dose groups (71.4% patients vs 26.2%, 22.2%, and 37.5%, respectively).

Phase 1 Clinical experience with oral panobinostat

Study [CLBH589B2102] is a multi-arm dose escalation phase I study of oral panobinostat in patients with hematologic malignancies. Two schedules of dosing of oral panobinostat are being evaluated in this study:

- Arm 1 – three-times-a-week every week N= 96
- Arm 2 - three-times-a-week every other week N= 56

Since severe thrombocytopenia is common in patients with acute myelogenous leukemia and other primary bone marrow disorders (e.g., high-risk MDS, AML) and is often treated supportively (i.e., with platelet transfusions), patients with these diseases are evaluated separately in Group X, from those patients who have better marrow function (e.g., patients with lymphomas and MM) who were enrolled in Group Y. The subgroups differ with respect to the definition of hematologic dose limiting toxicity (DLT); neutropenia and thrombocytopenia were considered DLT only in the subgroup Y.

Study results

Demographics: As of 31 December 2008, 152 were enrolled in the trial with 96 patients treated in subgroup X and 56 treated in subgroup Y. Data are available for 146 patients (Arm 1: 90 total [64 X subgroup, 26 Y subgroup]; Arm 2: 56 total [33 X subgroup, 23 Y subgroup]). Median age was 63.5 years (range:16-87 years).

Safety: In Arm 1 subgroup X, doses of 20 (n=8), 30 (n=8), 40 (n=10), and 60 mg (n=27) and 80 mg (n=11) have been evaluated. DLT of Grade 3 fatigue was noted at the 40 mg dose level (2 pts), and 60 mg dose level (2 pts). Patients with AML and high-risk MDS have been able to tolerate higher doses of panobinostat because thrombocytopenia is in general not considered dose-limiting. The principal DLT in this group of patients has been fatigue. A dose of 80 mg/day given three-times-a-week has proven

to generate excessive fatigue and QTcF prolongation. A dose of 60 mg three-times-a-week weekly produced grade 3 fatigue in 1/12 evaluable patients and was determined to be the MTD for Arm 1 subgroup X.
In Arm 1 subgroup Y, doses of 20 mg (n=1), 30 mg (n=4), 40 mg (n=16) and 60 mg (n=5) have been evaluated with grade 4 thrombocytopenia in the first 4 patients at the 60 mg dose level by the second week of therapy. The 60 mg dose was thus concluded to exceed the MTD. However, in the 16 patients treated at the 40 mg dose (14 of whom were considered evaluable), only 4 patients developed dose-limiting thrombocytopenia in the first cycle of treatment, and were successfully re-treated with a dose of 30 mg three-times-a-week. Based on this experience, 40 mg was declared the recommended phase II dose level in this group of patients with three-times-a-week continuous dosing.
In Arm 2 subgroup X, doses of 30 mg (n=6), 45 mg (n=9), 60 mg (n=9), and 80 mg (n=9) have been evaluated with DLTs in 4 patients treated at 80 mg (Grade 3 fatigue: 1 patient, Grade 3 QTcF: 1 patient, Grade 3 atrial fibrillation: 1 patient, and Grade 3 bilirubin: 1 patient). 80 mg cohort was closed with no further expansion in the lower dose level due to lack of efficacy relative to the Arm 1 subgroup X.
In Arm 2 subgroup Y, doses of 30 mg (n=1), 45 mg (n=7) and 60 mg (n=15) have been evaluated with grade 4 thrombocytopenia alone and associated with grade 3 fatigue in 2 patients treated at 60 mg, respectively. The dose level of 60 mg has been considered the MTD in this group of patients with the three-times-a-week every other week dosing.
Efficacy: A preliminary assessment of clinical activity has been conducted in various subtypes of hematologic malignancies included in this study. Data were available for 28 response-evaluable patients with relapsed/refractory Hodgkin's lymphoma. All of these patients were treated with doses ≥ 30 mg/dose, with either weekly (n=18) or every other week dosing (n=10). Eight out of 28 (29%) patients achieved metabolic PRs by positron emission tomography (PET) confirmed by computed tomography (CT)scan, 8 (29%) patients achieved metabolic PRs by PET, while 1 CR was observed both by PET and CT in a patient treated at 60 mg three-times-a-week every other week. Disease control was observed for up to 18+ cycles of therapy.
Study [CLBH589B2101] is a multi-arm dose escalation phase I study of oral panobinostat in patients with solid tumors and non-Hodgkin Lymphoma.
The study was initially designed to evaluate 2 dosing regimens:

- **Arm 1**: three-times-a-week every week in 28 day cycles N= 46
- **Arm 2**: continuous daily dosing (never opened to enrollment)

Protocol was subsequently amended to explore additional dosing schedules, based on PK/PD and safety data:

- **Arm 3:** three-times-a-week weekly every other week in 28 day cycles N= 23
- **Arm 5**: three-times-a-week or twice-a-week every week in 28 day cycles . N= 22

The study was also amended to characterize safety/tolerability, biologic activity, and PK profile of oral panobinostat in:

- **Arm 4**: three-times-a-week every week in 28 day cycles in metastatic melanoma patients N= 2
- **Arm 6**: three-times-a-week every week in 28 day cycles in CTCL patients N=1

At the dose of oral panobinostat 20 mg/day weekly, a pilot study to determine the food effect was conducted in 15 patients in Arm 1.

Study results

Demographics: A total of 94 patients, of whom 42 were female and 52 were male, with a median age of 61 years (range: 19-80), were enrolled in this study. One patient was enrolled twice with a different patient identification number.
Patients disposition: The primary reason for treatment discontinuation was PD (63.4% for patients with a primary diagnosis of CTCL and 84. 2 % for patients with other malignancy).
Safety: DLTs were experienced by patients who received doses ≥ 30 mg dose three times a week every week in this study.
Arm 3: Patients in Arm 3 were assigned to a dosing regimen of three-times-a-week every other week (q.o.w.). The first cohort in Arm 3 was treated at a dose level of 30 mg three-times-a-week q.o.w and the second cohort at 45 mg three-times-a-week q.o.w. Two patients were treated in cohort 2 and both

patients experienced a DLT in the first cycle. The dose level of 30 mg was determined to be the MTD for Arm 3.
Arm 5: Patients in Arm 5 were assigned to 30 mg, 45 mg or 60 mg dose of oral panobinostat given twice-a-week every week. In the 60 mg cohort, 1 patient was evaluable, and this patient experienced a DLT. As such, the MTD was determined to be 45 mg for Arm 5.

Human pharmacokinetics
After oral administration, panobinostat is rapidly absorbed with no observed lag phase. Maximum plasma concentrations were generally reached within 1 hour after oral dosing. The absolute bioavailability was 30% (data on file) and the mean (SD) half-life of panobinostat was comparable following i.v. and oral dosing ~15.0 (5) hours. Moderate drug accumulation was observed with oral three-times-a-week schedule but not with the weekly i.v. schedule (1.4-fold drug accumulation with oral three-times-a-week dosing), consistent with the terminal half-life of 15 hours and dosing interval.

Figure 0-1 Mean panobinostat plasma concentration versus time profiles following single oral or intravenous administration

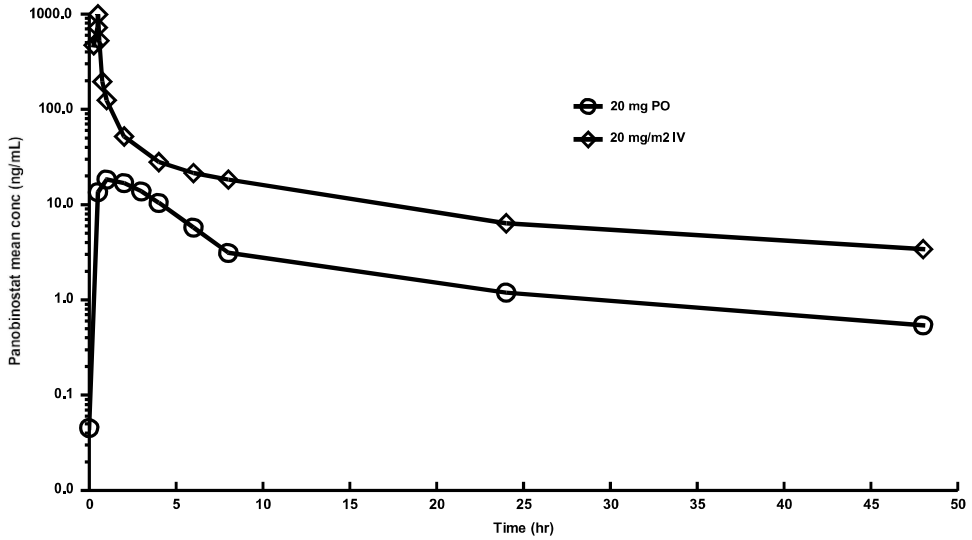


Table 0-2 Pharmacokinetic parameters of panobinostat in three ongoing Phase I studies [CLBH589A2101], [CLBH589B2101], and [CLBH589B2102]

Route of administration & Dose (No. of patients following single dose)	Mean (CV%) Single dose C_{max} (ng/mL)	Mean (CV%) Single dose AUC_{0-inf} (ng*hr/mL)	Mean (CV%) Multiple dose AUC_{0-48} (ng*hr/mL)
i.v. 20 mg/m^2 (n=31)	784 (45)	1041 (38)	n/a
p.o. 20 mg (n=45)	22.8 (58)	194 (58)	258 (65)
p.o. 30 mg (n=49)	36.2 (62)	267 (54)	279 (54)
p.o. 40 mg (n=24)	58.0 (59)	329 (77)	270 (59)
p.o. 60 mg (n=57)	66.1 (68)	362 (62)	306 (50)
p.o. 80 mg (n=18)	63.5 (58)	397 (49)	369 (52)
n/a: not applicable with weekly i.v. administration			

In vitro experiments suggested that the hepatic oxidative metabolism of panobinostat is mediated

primarily by cytochrome P450 (CYP)3A4, and to a lesser extent by CYP2D6 and CYP2C19. In addition to monooxygenation, hydrolysis of the hydroxamic sid chain (M43.5) were also found to be mediated (at least in-part) by the CYPs. These same metabolic pathways, were also observed in the recent human ADME and mass balance study [CLBH589B218].

Dose proportionality

A positive and linear dose-exposure relationship was found following single i.v. administration (1.2 to 20 mg/m^2, Rs = 0.83; p<0.0001). After oral dosing with 15 mg to 80 mg of panobinostat, dose-proportionality analysis indicated that systemic exposure increased nearly dose-proportionally at doses below 60 mg and there is less than proportional increase in AUC after 60 mg and 80 mg doses of panobinostat. It appears that absorption may become limiting at doses ≥ 60 mg of panobinostat.

Food Effect

Influence of food on panobinostat PK was evaluated in patients with advanced cancer who received 20 mg panobinostat twice a week and were randomized to receive panobinostat under fasting, high fat, and normal breakfast conditions [CLBH589B2111]. The overall exposure and inter-patient variability (CV 59%) in 34 patients remained unchanged with or without food, whereas C_{max} was transiently reduced by <45% and T_{max} prolonged by food (i.e., both normal and high fat breakfast). Since food did not alter the overall extent of absorption, food is unlikely to significantly impact panobinostat's systemic exposure in cancer patients. The findings from this formal food effect are consistent with the results from an earlier pilot food effect [CLBH589B2101] arm 1. Therefore, panobinostat can be administered without regard to food in future studies.

lectrocardiographic experience with panobinostat

Cardiac safety in patients with solid tumors and lymphomas

As of 31 December 2008, cardiac safety data were available for 202 patients who underwent intensive pre- and post-dose ECG monitoring. QTcF interval abnormalities are shown in Table 5-19. To date, an increase of > 30 msec (but less that 60 msec) from baseline and consistent across dose levels was the most prominent finding reported in 57 (28.2%) patients, the frequency of this finding being consistent across tested dose levels. An increase > 60 ms from baseline was observed in 9 (4.5%) patients. QTcF prolongation translating in an absolute value above 450 ms to ≤ 480 ms or > 480 ms to ≤ 500ms occurred in 34 (17%) and in 3 (1.5%) patients, respectively. Absolute QTcF prolongation above 500 ms was reported in one patient only treated at the dose of 20 mg/day.

Cardiac safety in patients with hematologic malignancies

As of 31 December 2008, cardiac safety data were available for 158 patients who underwent intensive pre- and post-dose ECG monitoring. To date, an increase of > 30 msec (but less that 60 msec) from baseline and consistent across dose levels was the most prominent finding reported in 50 (32%) patients, the frequency of this finding being consistent across tested dose levels. An increase > 60 ms from baseline was measured in 7 (4.4%) patients. QTcF prolongation translating in an absolute value above baseline to ≤ 480 ms or to ≤ 500ms occurred in 33 (20.9%) and in 4 (2.5%) of patients, respectively. Absolute QTcF prolongation above 500 ms was reported in 3 patients treated at the dose of 20 and 60 mg/day (1 and 2 patients, respectively .

Table 1-3 QTcF changes in patients receiving oral panobinostat three-times per week in hematologic malignancies

QTcF variable	20 mg/day [a] (N = 103) N* n(%)	30 mg/day[b] (N = 9) N* n(%)	40 mg/day [c] (N = 14) N* n(%)	60 mg/day [d] (N = 32) N* n(%)
QTcF increase from baseline > 30 and <= 60 ms	102 29(28.4)	9 4(44.4)	14 4(28.6)	32 13(40.6)
QTcF increase from baseline > 60 ms	102 4(3.9)	9 0(0.0)	14 0(0.0)	32 3(9.4)
Absolute QTcF > 450 and <= 480 ms	102 16(15.7)	9 3(33.3)	14 3(21.4)	32 11(34.4)
Absolute QTcF > 480 ms and <= 500 ms	102 3(2.9)	9 0(0.0)	14 0(0.0)	32 1(3.1)
Absolute QTcF > 500 ms	102 1(1.0)	9 0(0.0)	14 0(0.0)	32 2(6.3)

[a] Includes patients from [B2102] (group X, group Y, MM only), [B2202], [B2203], and [B2211]
[b, c, & d] Includes patients from [B2102] (group X, group Y, MM only)

ECG abnormalities were also evidenced during serial monitoring and central adjudication of their tracings. T-wave abnormalities (flat, inverted or biphasic T-waves) and ST segment depressed were the most frequent ECG abnormalities increasing in frequency by increasing the dose of panobinostat. The ECG abnormality table reports abnormalities with a cut-off of 5% in dose groups with n $\geq$ 25 patients having a 5% cutoff and of 25% when n < 25 patients in a given dose group.

Relationship between panobinostat plasma concentrations and QTcF

As presented in Figure 1-3 (i.v.) and Figure 1-4 (po) below, the maximum change of QTcF from baseline does not coincide with the peak plasma concentration-time course of panobinostat for either route of administrations suggesting a possible delayed effect. It is noteworthy (as shown in Table 1-3) that the mean maximum concentration (C_{max}) and overall exposure (AUC) for the oral formulation is at least 30-fold and 5-fold, respectively lower than that has been seen with intravenous panobinostat. It does not appear that QTcF change is directly related to panobinostat plasma concentrations.

Figure 0-2 QTcF change from baseline over time vs. panobinostat conc-time course following the first intravenous panobinostat weekly doses

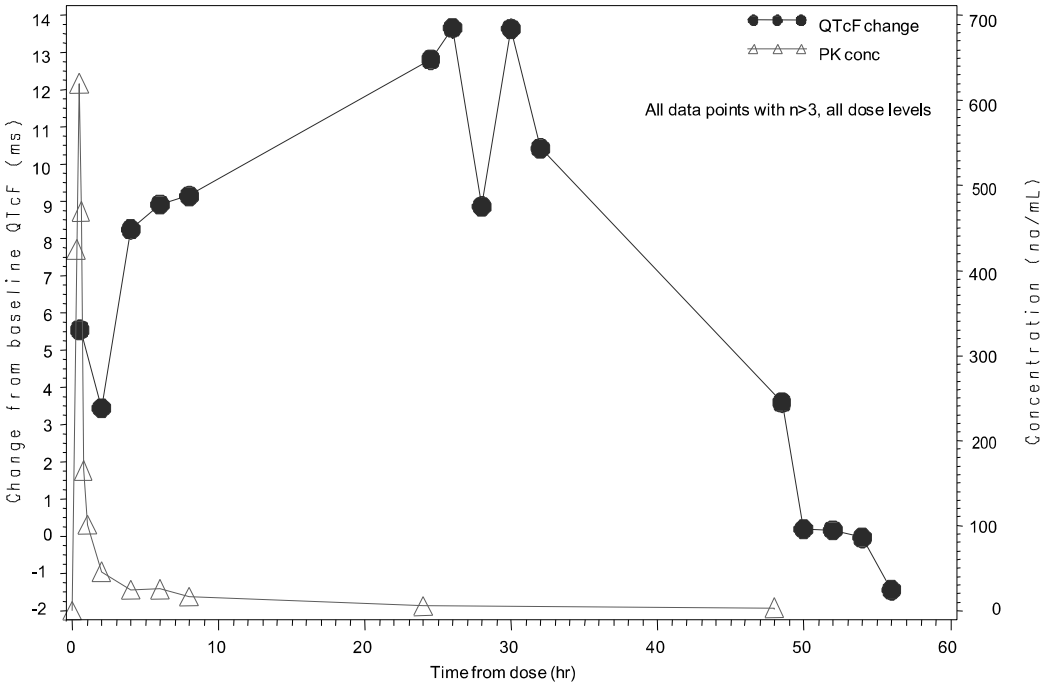
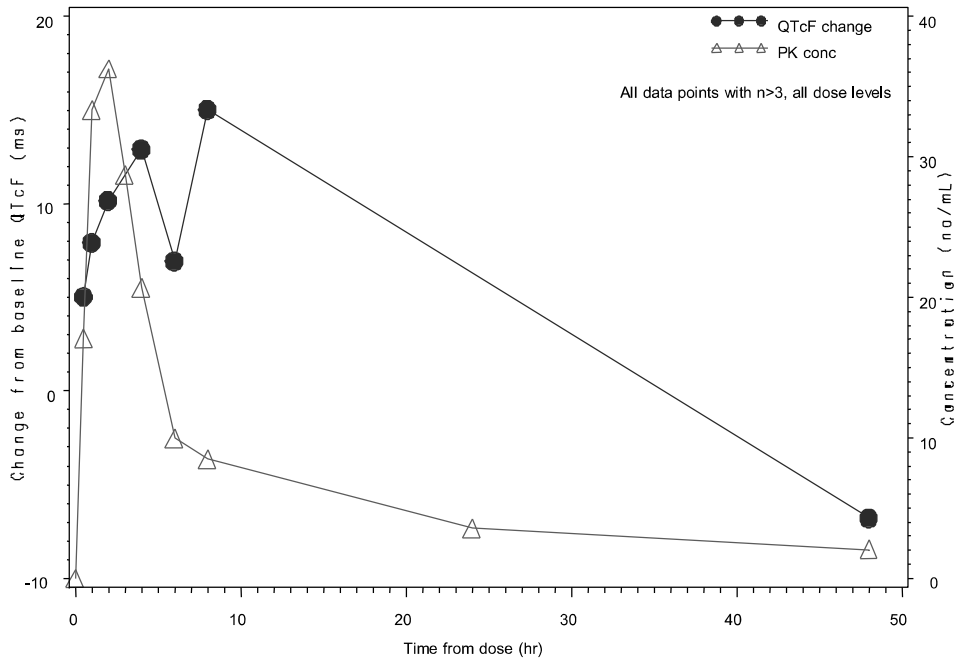


Figure 0-3 QTcF change from baseline over time vs. panobinostat conc-time course following the first oral panobinostat doses of a MWF schedule



3.2 ETOPOSIDE

- **Common Tradenames *(See Complete Tradename Listing)***
  - VEPESID
- **Class**
  - antineoplastic
  - mitotic inhibitor
- **Dosage, Adult (usual)**
  - Lung cancer, small cell: Range, 35 mg/m$^{(2)}$/day IV for 4 days, to 50 mg/m$^{(2)}$/day IV for 5 days; in combination with other approved chemotherapeutic agents; repeat at 3-4 week intervals
  - Lung cancer, small cell: ORAL dose is 2 times the IV dose rounded to the nearest 50 mg (VePesid^{R})
  - Bone marrow transplantation: 2 g/m^2 IV over 24 hrs followed by filgrastim has been used for peripheral blood progenitor cell mobilization
  - Testicular cancer: range, 50-100 mg/m^2/day IV, days 1-5 to 100 mg/m^2/day IV on days 1,3, and 5; in combination with other approved chemotherapeutic agents; repeat at 3-4 week intervals
- **Administration**
  - administer over 30-60 min to avoid hypotension; avoid skin contact; do not use acrylic or ABS plastic devices with undiluted VePesid $^{(R)}$ for injection
  - store in the refrigerator
  - dilute with D5W or NS to conc of 0.2-0.4 mg/mL, stability 24 hrs; MAXIMUM concentration 0.4 mg/mL
- **Monitoring**
  - platelet count, hemoglobin, WBC count, and differential at start of therapy and prior to each subsequent cycle
  - monitor liver function tests
- **How Supplied**
  - 50 MG CAPSULE
  - 20 MG/ML SOLUTION FOR INJECTION

3.3 MESNA

- **Common Tradenames *(See Complete Tradename Listing)***
  - Mesnex
- **Class**
  - Antineoplastic Agent
- **Dosage, Adult (usual)**
  - Cyclophosphamide adverse reaction, High dose; Prophylaxis - Hemorrhagic cystitis; Prophylaxis: 40% IV (W/W) of cyclophosphamide dose at 0,3,6,9 hr and IV fluids
  - Cyclophosphamide adverse reaction, Low dose; Prophylaxis - Hemorrhagic cystitis; Prophylaxis: 20 mg/kg ORALLY every 3-4 hr
  - Hemorrhagic cystitis; Prophylaxis - Ifosfamide adverse reaction; Prophylaxis: bolus IV regimen, IV bolus 20% of ifosfamide dose (w/w) at 0, 4, 8 hr
  - Hemorrhagic cystitis; Prophylaxis - Ifosfamide adverse reaction; Prophylaxis: oral tablet regimen, IV bolus 20% of ifosfamide dose (w/w) at time of infusion, tablets 40% of ifosfamide dose at 2, 6 hr
  - Hemorrhagic cystitis; Prophylaxis - Ifosfamide adverse reaction; Prophylaxis: continuous IV regimen (non-FDA approved regimen), bolus dose (20% total ifosfamide dose), then 40% of ifosfamide CIV
- **Dosage, Pediatric, (usual)**
  - safety and efficacy of mesna tablets have no been established in children
  - Hemorrhagic cystitis; Prophylaxis - Ifosfamide adverse reaction; Prophylaxis: IV bolus 20% of ifosfamide dose (w/w) at 0, 4, 8 hr
- **Administration**
  - total daily dose mesna: IV regimen 60%; IV:ORAL regimen 100%
  - due to the benzyl alcohol content, the MULTIDOSE vial should not be used in neonates or infants and should be used with caution in older pediatric patients
  - IV mesna should continue 12-24 hr after the completion of ifosfamide
  - SC route has been used
  - patients who vomit within 2 hr of taking oral mesna should repeat the dose or receive IV mesna
- **Monitoring**
  - monitor nausea, vomiting, and diarrhea (occur with higher doses (80 mg/kg))
- **How Supplied**
  - Intravenous Solution: 100 MG/ML
  - Oral Tablet: 400 MG

3.4 IFOSFAMIDE

- **Common Tradenames *(See Complete Tradename Listing)***
  - Ifex
- **Class**
  - Alkylating Agent
  - Antineoplastic Agent
  - Nitrogen Mustard
- **Dosage, Adult (usual)**
  - Germ cell tumor, Third-line (in combination with other antineoplastic agents) - Primary malignant neoplasm of testis, Third-line (in combination with other antineoplastic agents): 1.2 g/m(2) IV daily for 5 days repeated every 3 weeks; use with a prophylactic agent for hemorrhagic cystitis
  - Head and neck cancer: see specific protocols for dosage
  - Non-Hodgkin's lymphoma: see specific protocols for dosage

- Sarcoma: see specific protocols for dosage

- **Administration**
  - administer hydration (minimum 2 L/day) plus mesna to limit urotoxicity; recommended IV mesna dosing is 20% ifosfamide dosage (w/w) at the time of the ifosfamide infusion, 4 and 8 hrs after every ifosfamide dose
  - reconstitute with SWFI/BWFI to a concentration of 50 mg/ml; dilute further to 0.6-20 mg/mL in D5W, NS, LR, SWFI
  - IV infusion over at least 30 minutes
- **Monitoring**
  - monitor serum/urine chemistries including phosphorous, alkaline phosphatase, and other appropriate laboratory studies
  - complete blood counts prior to each administration; hold further therapy if white cell count is less than2,000 or platelets less than50,000
  - urinalysis is recommended prior to each dose; withhold doses until recovery if hematuria greater than 10 red cells per high power field is found
- **How Supplied**
  - Intravenous Powder for Solution: 1 GM, 3 GM

3.5 CARBOPLATIN

- **Common Tradenames *(See Complete Tradename Listing)***
  - Paraplatin
  - Paraplatin NovaPlus
- **Class**
  - Antineoplastic Agent
  - Platinum Coordination Complex
  -
- **Administration**
  - do NOT use with infusion sets/needles containing aluminum
  - alternative dosing regimen: Calvert formula recommendations- dose(mg)= target (AUC) x (GFR + 25); area under the curve (AUC), glomerular filtration rate (GFR)
  -
- **Monitoring**
  - complete blood counts (CBC) should be taken before each course of treatment; the white blood cell count and the platelet count should be greater than or equal to 4000/mm(3) and 100,000/mm(3), respectively, before retreatment; routine CBCs should be checked once or twice between each course of carboplatin administration-doses should be reduced if severe myelosuppression occurs
  - renal function should be monitored, especially in patients with preexisting renal dysfunction or prior aminoglycoside therapy; baseline values of blood urea nitrogen (BUN), serum creatinine, and creatinine clearance should be established; BUN and serum creatinine should be remeasured before each course of carboplatin
  - serum electrolyte levels (sodium, calcium, magnesium, and potassium) should be measured at baseline, between courses of therapy weekly, and immediately before subsequent courses; decreases in these serum electrolytes are usually mild and reversible
  - patients who have received prior therapy with cisplatin or have had previous hearing loss should have baseline audiometry testing before receiving carboplatin; repeat testing should be performed if hearing loss is noted
  - liver function tests should be evaluated at baseline and before each course of carboplatin
  -

- **How Supplied**
  - Intravenous Powder for Solution: 50 MG, 150 MG, 450 MG
    - Intravenous Solution: 10 MG/ML

4.1 PATIENTS ELIGIBILITY

4.2 Inclusion Criteria

1. Histologically confirmed classical Hodgkin lymphoma (nodular sclerosis, mixed cellularity, or lymphocyte-rich classical HL).
2. Patients must have failed (relapsed or refractory) front-line standard anthracycline-containing regimen, such as ABVD, Stanford V, or BEACOPP.
3. Bidimensionally measurable disease with at least 1 lesion ≥ 2.0 cm in a single dimension
4. Acceptable hematologic status:
   - Hemoglobin ≥ 9.0 g/dL
   - Absolute neutrophil count ≥ 1500 cells/mm^3
   - Platelet count ≥ 100,000 cells/mm^3
5. Normal serum K+, Mg+, PO4, and total Ca++ (pre-treatment abnormal values may be therapeutically corrected before starting therapy and must be documented as normal or if abnormal values persist must be documented as clinically insignificant). Albumin should be ≥ 3
6. Pre-study WHO performance status of 0, 1, or 2
7. Age ≥ 16 years
8. Voluntary signed IRB approved consent informed before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
9. Patients of reproductive potential (female of child bearing potential has not been postmenopausal for at least 12 consecutive months or not surgically sterile; male of child bearing potential has not been surgically sterile)must follow accepted birth control methods (e.g. barrier method) during treatment.
10. Clinically euthyroid. Note: Patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism.
11. Baseline MUGA or ECHO must demonstrate LVEF >/= 50%.

4.3 Exclusion Criteria

1. Lymphocyte predominant histology
2. More than one prior chemotherapy regimens.
3. Prior therapy with other HDAC inhibitors, including valproic acid
4. Prior therapy with heat shock protein (HSP)-90 inhibitors
5. Prior stem cell transplant
6. Abnormal liver function:
   - Bilirubin > 2.0 mg/dL (26 µmol/L)
   - Alkaline phosphatase > 2 x upper limits of normal (ULN)
   - AST (SGOT) and/or ALT > 2 x ULN
7. Serum creatinine >1.5 mg/dl
8. Presence of CNS involvement with Hodgkin lymphoma
9. Presence of HIV infection or AIDS.

10. Another primary malignancy (other than squamous cell and basal cell carcinoma of the skin, in situ carcinoma of the cervix, or treated prostate cancer with a stable PSA) for which the patient has not been disease-free for at least 3 years.
11. Serious nonmalignant disease (e.g., congestive heart failure, hydronephrosis); active uncontrolled bacterial, viral, or fungal infections; or other conditions which would compromise protocol objectives in the opinion of the investigator.
12. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
    - History or presence of sustained ventricular tachyarrhythmia.
    - Any history of ventricular fibrillation or torsade de pointes
    - Bradycardia defined as HR< 50 bpm. Patients with pacemakers are eligible if HR ≥ 50 bpm.
    - Screening ECG with a QTc > 450 msec
    - Right bundle branch block + left anterior hemiblock (bifascicular block)
    - Patients with myocardial infarction or unstable angina ≤ 6 months prior to starting study drug
    - Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV , uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)

13. Female subject is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening, unless the female has recently (within 8 weeks) undergone egg harvest, which would result in the (β-hCG) test to be elevated without pregnancy. Pregnancy testing is not required for post-menopausal or surgically sterilized women.
14. Patient has received other investigational drugs within 14 days before enrollment or who have not recovered from side effects of those therapies.
15. Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
16. Impairment of GI function or GI disease that may significantly alter the absorption of panobinostat
17. Patients with diarrhea > CTCAE V.4 grade 2
18. Patients using medications that have a relative risk of prolonging the QT interval or inducing torsade de pointes if treatment cannot be discontinued or switched to a different medication prior to starting study drug
19. Patients who have received either immunotherapy within ≤ 8 weeks; chemotherapy within ≤ 3 weeks; or radiation therapy to > 30% of marrow-bearing bone within ≤ 2 weeks prior to starting study treatment; or who have not yet recovered from side effects of such therapies.
20. Patients who have undergone major surgery ≤ 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy

5.1 TREATMENT PLAN

5.2 Phase-I

5.2.1 This is an open-label, non-randomized single-arm, Phase I, dose escalation trial to define the safety profile, the maximum tolerated dose (MTD), and the antitumor activity of panobinostat plus ICE chemotherapy administered orally in patients with relapsed/refractory classical Hodgkin lymphoma (HL).

5.2.2 Study assessments will include monitoring of all toxicities and adverse events, and objective tumor measurements. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 will be used for grading adverse events and all toxicities.

The phase-I portion of this study will conclude once the MTD has been reached, and the toxicity profile has been defined. The phase-II doses will be based on data obtained from this phase-I portion of the study.

5.1.3 Phase-I dose levels

Panobinostat + ICE combination therapy will be administered at the dose level assigned to each cohort, as outlined in Table 5. Each ICE cycle is considered to be 14 days (2 weeks). A tumor response assessment will be done within 7-13 days of completion of 3 cycles of ICE using the Revised Response Criteria for Malignant Lymphoma. Patients with a complete response (CR) or partial response (PR) will be considered for stem cell transplantation, otherwise they will be removed from the study.

Table-5: Study design for the phase-I

Dose Level	*ICE chemotherapy Day 1 and repeat every 14-days*	*PANOBINOSTAT (mg, orally) 3 times per week*
-1	*See Table 5.2*	*10*
0	*See Table 5.2*	*20*
1	*See Table 5.2*	*30*

5.1.4 Panobinostat is given only during cycles 1 and 2 of ICE according to Table 5.1. Cycle 3 of ICE will be given without panobinostat.

5.1.5 Investigational therapy: Panobinostat (LBH589).

Panobinostat will be provided by Novartis. Oral Panobinostat will be supplied as 5-mg or 20-mg hard gelatin capsules.

Medication labels will comply with US legal requirements and be printed in English. They will supply no information about the patient. The storage conditions for study drug will be described on the medication label.

During the study, Panobinostat will be self-administered (by the patients themselves) orally three times per week.

For cycle 1 of ICE: Panobinostat will be administered starting day -6 and ICE on day 1 as outlined in Table 5.1:

Patients should be instructed to take their oral dose of Panobinostat around the same time each day. Each dose of Panobinostat should be taken with an 8 oz / 240 ml glass of water. Patients should be instructed to swallow the capsules whole and not chew them. Patients must avoid grapefruit or grapefruit juice and seville (sour) oranges during the entire study.

If the patient forgets to take his/her dose on a scheduled treatment day, then he/she should take Panobinostat on that same day within 12 hours after the missed dose if possible. After more than 12 hours, that day's dose should be withheld, and the patient should wait to take Panobinostat until the next scheduled treatment day (i.e., patients should be instructed not to try to make-up the missed dose after 12 hours). The patient should then continue treatment with the original dosing schedule. A pill diary will be provided to the subject for documentation of dosing for each cycle.

The investigator should instruct the patient to take the study drug exactly as prescribed (promote compliance). All dosages prescribed and dispensed to the patient and all dose changes during the study should be recorded. All used and unused study drug will be returned to the study site personnel.

5.1.6 Dose escalation

Standard doses of ICE chemotherapy will be used and fixed, while panobinostat doses will be escalated (Tables 5, 5.1, and 5.2). Initially, 3 patients will be treated at each dose level and will be monitored for dose limiting toxicities (DLT) for 14 days from the first dose of ICE. If no DLTs are observed in those 3 patients at the end of the observation period, escalation to the next dose level may commence. If a DLT is observed in 1 of the first 3 patients, the cohort will be expanded to a maximum of 6 patients. If 2 or more DLTs are observed in any cohort, no further escalation will take place. The maximum tolerated dose (MTD) will have been exceeded, and the preceding dose level will be recommended for the Phase-II portion of this study. If DLTs are observed in 0 dose level, -1 dose level will be evaluated for DLTs before recommending it as MTD.

5.1.7 Opening of Subsequent Cohorts

The third or sixth patient in each cohort must be observed for 21 days after the first day of panobinostat (14 days after the first dose of ICE) before dosing in the next cohort can begin. If any patient registered within a cohort does not complete at least one cycle of treatment, that patient will be replaced unless discontinuation is for DLT.

Prior to advancing/changing dose levels a cohort summary must be completed and submitted to the clinical research monitor.

Upon review of clinical outcome after enrolling 10 patients in an expansion cohort in schedule A (Table 5.1), thrombocytopenia was considered profound. Therefore, a new schedule B (Table 5.2) with less doses of panobinostat is being investigated in an expansion cohort of phase I to accrue 10 patients.

5.1.8 Dose Limiting Toxicity

The Principal Investigator will document the overall toxicity profile in detail before deciding whether to initiate cohort expansion, or dose escalation. In the event that Grade 3 or 4 adverse events are obviously unrelated to study drug and thus not dose-limiting, the Principal Investigator will determine whether dose escalation or cohort expansion is required.

5.1.9 Non-hematologic Toxicity

For non-hematologic toxicities, DLT will be defined as any CTCAE v4.0 Grade 3 or greater toxicity except for:
- Grade 3 fatigue.
- Grade 3 or 4 nausea and vomiting lasting less than 72 hours after the last dose of chemotherapy.
- Grade 3 non-hematologic laboratory abnormalities that resolve to Grade 1 or baseline (if the patient entered the study with existing toxicity) within 14 days of the first dose of ICE chemotherapy.

5.1.10 Hematologic Toxicity

DLT for hematologic toxicity, using CTCAE v4.0, will be defined as:
- Grade 4 neutropenia lasting greater than 14 days.
- Grade 4 febrile neutropenia.
- Grade 4 platelet count (<25,000/mm3) at any time, lasting greater than 14 days.

5.1.11 Dose Elimination/Holding/Reduction

A scheduled dose of panobinostat may be held no more than 3 consecutive doses in a 2 week cycle of ICE and no more than 6 consecutive doses in a 3 week cycle of ICE. If it is held longer than this specified time, that patient will be removed from study.

For example, if a patient is delayed 1 week to receive a cycle of ICE then 6 consecutive doses of panobinostat may be missed but if ICE is administered every 2 weeks on schedule then no more than 3 consecutive doses of panobinostat may be missed.

For those patients entered in the expanded cohort (Dosing Schedule B) of adjusted panobinostat dosing, panobinostat will be self administered by patient 3x/week starting D-6 and will continue through D5 and be held until start of next cycle of ICE. If ICE is held due to AE and given every 3 weeks, a patient cannot miss more than 6 consecutive doses of panobinostat or will be removed from study.

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5.1.13 Maximum Tolerated Dose (MTD)

The MTD will be the highest dose at which no more than 1 in 6 of the patients in the cohort experiences one or more DLTs in the first treatment cycle (21 days from the first dose of panobinostat and 14 days from the first dose of ICE).

5.2 Phase-II

5.2.1 The starting dose of panobinostat will be based on the data generated from the phase-I portion of this study.

5.2.2 Patients will be randomized by MDACC to arm 1 (ICE) or arm 2 (Panobinostat + ICE) as shown in Table 5.2.

5.2.3 For cycle 1 of the panobinostat arm, panobinostat will be given on day -6. (See Fig1)

5.2.4 Cycle 3 of both arms will be ICE alone (to minimize any potential effect on stem cell collection

Table 5.1
Schedule A

Day of cycle	HDACi	Chemotherapy(ICE)			Growth factor
-6	Panobinostat				
-5					
-4	Panobinostat				
-3					
-2	Panobinostat				
-1					
0					
1	Panobinostat	Ifex/Mesna	Carboplatin	Etoposide	
2				Etoposide	
3	Panobinostat			Etoposide	
4					start growth factor support
5	Panobinostat				
6					
7					
8	Panobinostat				
9					
10	Panobinostat				
11					
12	Panobinostat				
13					
14					

Table 5.1.1 Dosing Schedule B

Day of cycle	HDACi	Chemotherapy(ICE)			Growth factor
-6	Panobinostat				
-5					
-4	Panobinostat				
-3					
-2	Panobinostat				
-1					
0					
1	Panobinostat	Ifex/Mesna	Carboplatin	Etoposide	
2				Etoposide	
3	Panobinostat			Etoposide	
4					start growth factor support
5	Panobinostat				
6					
7					
8					
9					
10					
11					
12					
13					
14					

5.2.5 The doses of each drug are shown in the following table 5.2.

Table 5.2. Doses of ICE vs panobinostat + ICE				
	Arm 1 (ICE)	**Arm 2 (Panobinostat + ICE) Schedule B**		
Day	**Drug**	**Drug**	**Dose**	**Infusion time**
Starting day -6 and given 3 times per week during cycles 1 and 2		PANOBINOSTAT (LBH589)	MTD determined by phase I	Oral
1	Ifosfamide + Mesna	Ifosfamide + Mesna	5 grams/m2 equal dose of each	IV continuous infusion over 24 hours
2	Mesna	Mesna	2 grams/m2	IV continuous infusion over 12 hours
1	Carboplatin	Carboplatin	standard dose (target AUC=5mg/ml /min)	IV over 1 hr
1, 2, 3	Etoposide	Etoposide	100 mg/m2/day	IV over 2 hours
4**(12-48 hrs after completion of ICE)	growth factor support	growth factor support	Standard dose	

*** A window of 2 days will be allowed when administering ICE chemotherapy**

**If Cycle 3 is to be used for stem cell mobilization, growth factor can be given according to the schedule of stem cell harvest.ie start of growth factor can be >/= 48 hrs.

5.2.6 Patients will receive 3 cycles of ICE every 14 (+/- 2) days, with growth factor support.

5.2.7 Dose modification is allowed as per Table 7.1. ICE treatment should be delayed until ANC> 1,000 /µL, and platelet count > 75,000/µL. Dose delays of ICE >14 days will result in removing the patient from the study.

5.3.8 Repeat imaging studies after 3 cycles.

6.0 TREATMENTEVALUATION:

6.1 Pre-Treatment Evaluation

Within 30 days (+/- 7days) of starting therapy

6.1.1 Imaging studies (a chest x-ray (CXR), CT scans of the head and neck, chest and abdomen and pelvis, and a PET scan).
6.1.2 Bone marrow biopsy, if clinically indicated.
6.1.3 Serum HIV test if the patient has risk factors or did not have one within the past 12 months.
6.1.4 ECHO/MUGA
6.1.5 Medical History Assessment

Within 7 days (+/- 2) of starting therapy

6.1.7 CBC with differential, chemistry (albumin, BUN, glucose, ALT/SGPT, AST/SGOT, alkaline phosphatase, LDH, total bilirubin, creatinine, sodium, potassium, calcium, magnesium
6.1.8 EKG
6.1.9 Physical examination, vital signs and weight
6.1.10 Serum pregnancy test for females of child bearing potential

6.2 Evaluation During The Study:

- Within 7 days of starting each cycle of ICE therapy: physical examination, CBC with differential, SMA and electrolytes.
- Blood (about 2 1/2 teaspoons) will be collected for routine tests.
- Weekly CBC, and electrolytes while on study.
- Toxicity evaluation within 7 days of each ICE therapy.
- Repeat imaging studies after 3 cycles of ICE. (7-13 days after completion of ICE)
- Bone marrow biopsy (if it was positive before starting therapy) and PET scan should be performed to confirm CRs
- EKG 1 (+/- 2 days) per table 6.3
-
- All patients who receive at least one dose of panobinostat will be evaluable for response and toxicity unless the reason for premature termination of the study is reasons other than progression or toxicity (such as poor compliance or patient withdrawal).
- The patient completes the study upon response evaluation with PET scan after 3 cycles of treatment, unless toxicity of grade 3 or greater related to the treatment is ongoing, in which case until it is resolved.

6.2.1 End-of-Treatment Visit (after completing 3 cycles of ICE) or Withdrawal visit

- Physical exam, including measurement of your weight and vital signs.
- EKG

Patients who benefit from the study drug or the combination, if not eligible for stem cell transplant (SCT), should be allowed to continue on study with the approval of principal investigator (PI) and the attending physician.

6.3 Cardiac assessments

A screening 12-lead ECG will be performed to assess study eligibility. Additional 12-lead ECGs will be performed at a minimum at scheduled time points as indicated in Table 6-3.

Table 6-3: Cardiac assessment monitoring schedule

Cycle	Day of cycle	ECG monitoring
Screening		Single ECG to assess eligibility
Cycle 1	-6	Single pre-dose ECG
	-6	Single Post-dose (2 ± 0.5 hours)
	-2	Single pre-dose ECG
	-2	Single Post-dose (2 ± 0.5 hours)
Cycle 2 and all subsequent cycles	1	Single pre-dose ECG
End of treatment	Last	Single ECG

7.1 Criteria for Dosing Modifications

(For Phase II part we suggest the following dose reduction schedule as incorporated in other ongoing studies)

Investigators can use their discretion when making dose-reduction decisions for ICE based on the package insert recommendations unless otherwise specified in the guidelines in Table 7-1 below. In addition Patients should be discontinued from study treatment if they require a dose delay > 14 days from the intended day of the next scheduled dose (for all events other than prolonged QTcF). If a patient cannot be dosed due to prolonged QTcF interval for more than 7 days since last dose, patient should be discontinued from study. All cardiac events should be treated as per the local standard of care and referred to a specialist by the investigator if clinically indicated. Any final decisions concerning any dose modification / interruptions or patient discontinuing study drug permanently should be made by the investigator based on QTcF calculations assessed.
Nothing in this protocol or the underlying agreement shall be deemed to restrict or interfere with the independent medical judgment and decision making abilities of the investigator or other M.D. Anderson personnel.

Table 7-1 Criteria for dosing delays, dose-reductions, and re-initiation of treatment due to study drug-related toxicity (excluding QT prolongation) (only applies to Phase II)

Worst Toxicity **CTCAE Grade**** unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)***
HEMATOLOGICAL TOXICITIES		
Thrombocytopenia	Grade 4 (< 25 x 10^9/L)	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 2, or baseline, then: • restart panobinostat reduced by one dose level • If event recurs, hold drug and resume at next lower dose level*
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L)	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 3, or baseline, then: • Restart panobinostat reduced by one dose level • If event recurs, hold drug and resume at next lower dose level*
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Temporarily discontinue panobinostat dosing until fever resolved and ANC ≤ grade 2, then restart panobinostat reduced by one dose level
NON-HEMATOLOGICAL TOXICITIES		
CARDIAC		
Cardiac - Prolonged QT interval**		Please refer to Section 7.2
GASTROINTESTINAL		
Diarrhea	Grade 2 (4-6 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then restart at an unchanged dose level - If event recurs, hold drug and resume at next lower dose level*
	Grade 3 (≥ 7 stools/day over baseline, etc) despite the use of optimal antidiarrheal medications	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then restart panobinostat reduced by one dose level • If event recurs, hold drug and resume at next lower dose level*
	Grade 4 (life-threatening consequences, hemodynamic collapse, etc) despite the use of optimal antidiarrheal medications	Discontinue panobinostat dosing
Vomiting/Nausea***	Grade 1 & 2 not requiring treatment or controlled using standard anti-emetics	Maintain dose level
	Grade 3 or 4 vomiting or Grade 3 nausea that cannot be controlled despite the use of standard anti-emetics	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then restart panobinostat reduced by one dose level • If event recurs, hold drug and resume at next lower dose level*
Fatigue		

Worst Toxicity **CTCAE Grade**** unless otherwise specified (Value)**		**Dose Modification Guidelines** **At any time during a cycle of therapy (including intended day of dosing)***
Fatigue	Grade 3 or 4	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 2, or baseline, then: • restart panobinostat reduced by one dose level • If event recurs, hold drug and resume at next lower dose level*
HEPATIC		
Total Bilirubin	Grade 3 or 4	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 2, or baseline, then restart panobinostat reduced by one dose level
Note: If Grade 3 or Grade 4 hyperbilirubinemia is due to the indirect component only, and hemolysis as the etiology has been ruled out as per institutional guidelines (e.g., review of peripheral blood smear and haptoglobin determination), then reduction of one dose level and continuation of treatment is at the discretion of the Investigator.		
AST/SGOT, ALT/SGPT	> 5-10 x ULN	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1 or baseline, then restart at an unchanged dose level • If event recurs, hold drug and resume at next lower dose level*
	> 10 x ULN	Temporarily discontinue panobinostat dosing until resolved to ≤ grade 1, or baseline, then: • restart panobinostat reduced by one dose level • If event recurs, hold drug and resume at next lower dose level*
All dose modifications should be based on the worst preceding toxicity. * For each dose reduction, should the event recur after resuming drug, further dose reductions are permitted ** It is critical that electrolyte abnormalities be followed closely and corrected prior to dosing *** See also concomitant medication section 7.3 **** Common Terminology Criteria for Adverse Events (CTCAE Version 4.0)		

General guidelines for dose modifications due to adverse events related to study drug are provided below.

Grade 3 or 4 non-hematologic toxicity

Patients experiencing new (or treatment emergent) CTCAE grade 3 or 4 non-hematologic AEs not listed in Table 7-1, should have their treatment temporarily discontinued until the adverse event resolves to ≤ CTCAE grade 1 or baseline unless otherwise specified in Table 7-1. If the AE was considered related to panobinostat, the drug should then be restarted at one dose level lower. If the AE was considered not related to panobinostat, then therapy may be restarted (when the AE resolves to ≤ grade 1 or baseline) at the current dose and schedule

Management of diarrhea

Patients should be instructed to contact their physician at the onset of diarrhea. Each patient should be instructed to have loperamide readily available and to begin treatment for diarrhea at the first episode of poorly formed or loose stools or the earliest onset of bowel movements more frequent than normally expected for the patient.

Loperamide 4 mg should be taken at the first loose stool or more frequent than usual bowel movements, followed by 2 mg as needed, no more frequently than every 4 hours, not to exceed a total of 16 mg in 24 hours. Patients with diarrhea ≥ grade 2 despite this loperamide regimen should interrupt treatment with panobinostat as described in Table 7-1. If the above regimen is inadequate then additional evaluation and treatment should be pursued as medically indicated. Replacement i.v. fluids and electrolytes may be used as appropriate. Additional treatment should be provided in accordance with institutional standard of care and/or local guidelines.
Premedication with loperamide is not recommended.
The use of drugs with laxative properties should be avoided because of the potential for exacerbation of diarrhea. Patients should be advised to contact their physician to discuss any laxative use.

7.2 Dose modifications for prolonged QTcF interval

All cardiac events should be treated as per the local standard of care and referred to a specialist if clinically indicated. Any final decisions concerning dose modifications or permanently discontinuing the patient from study drug due to QTcF prolongation will be based on the assessment of the Investigator. Any plan to deviate from these guidelines should be previously discussed and agreed upon by the investigator. If a patient cannot be dosed due to prolonged QTcF for more than 7 days since last dose, patient should be discontinued from study.

Table 7-2 Criteria for dosing delays, dose-reductions, and re-initiation of treatment due to study drug-related QTcF abnormalities

ECGs to be performed at specified time point	**Abnormality Noted**	Dose Modification Guideline - At any time during a cycle of therapy (including intended day of dosing)
Cycle 1 dose modifications		
Pre-dose for each cycle on day 1 for cycle 2 and 3 and for day -6 and -2 on cycle 1 only:	If Day 1 for cycles 2 and 3 and day -6 and -2 for cycle 1 only: A single ECG obtained shows QTcF > 460 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. Notify Investigator immediately for prompt review. If abnormality noted on Day 1 of Cycle 2 and 3 and day -6 and -2 for cycle 1 only: Delay dose at least 3 days and repeat pre-dose ECG. If the pre-dose ECG: **Do not meet** criteria again, discontinue patient from study. **Do meet** criteria for dosing; administer study drug treatment at. **Do meet** pre-dose ECG criteria for dosing and QT prolongation determined to be related to study drug, resume study drug treatment with a dose reduction of 10 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), and 6-hours post-dose (x3) on the next scheduled dosing day after the reduced dose is given.*
	A single ECG obtained shows QTcF >480 msec to ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. Notify Investigator immediately for prompt review. **Discontinue** patient from study therapy

Cycle 1 day -6 and -2 only, post-dose:	A single post-dose ECG obtained shows QTcF ≥ 480 msec to < 500 msec OR > 60 msec increase from baseline	If abnormality noted on Day 6 or -2 of Cycle 1 (post- dose): Check and correct the patient's serum potassium, magnesium, calcium and phosphorus immediately, as well as evaluate con-meds. Monitor ECG hourly or by telemetry until at least 2 consecutive hourly ECGs performed at least 6 hours post dose are <480. Notify Investigator immediately for prompt review. Delay dose 3 days and repeat pre-dose ECG. If the pre-dose ECG: **Do not meet** pre-dose ECG criteria for dosing (pre-dose ECGs have a QTcF ≤ 460 msec), discontinue patient from study. **Do meet** pre-dose ECG criteria for dosing (pre-dose ECGs have a QTcF ≤ 460 msec) and QT prolongation determined to be related to study drug, resume study drug treatment with a dose reduction of 10 mg. If however, it was determined that the QT prolongation was secondary to electrolyte abnormalities or con-meds, continue at the same dose level. Repeat ECGs - pre-dose (x3), 3-hours post-dose (x3), and 6-hours post-dose (x3) on the next scheduled dosing day after the reduced dose is given*.
	A single ECG obtained shows QTcF ≥ 500 msec	**Check and correct** the patient's serum potassium, magnesium, calcium and phosphorus immediately. Notify Investigator immediately for prompt review. **Discontinue** patient from study therapy

7.3 Other concomitant medications

Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded. In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- Any medications Appendix 1 which may cause QTc prolongation or inducing Torsades de pointes should not be used.
- Any medications that have the potential to alter serum electrolytes (e.g., diuretics) should be monitored very closely for electrolyte abnormalities as these can contribute to the risk of QT prolongation and ventricular arrhythmias.
- No other investigational therapy should be given to patients
- No anticancer treatments (including radiation therapy) other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Granulocyte growth factors (e.g.G-CSF and GM-CSF) will be administered routinely to prevent and treat neutropenia.

- Concomitant use of CYP3A4 inhibitors with panobinostat should be used with caution due to a potential increase in panobinostat exposure during concomitant treatment with these drugs. Please refer to Appendix 2
- Medications known to be substrates of the isoenzyme CYP2D6 should be used with caution with panobinostat as panobinostat can inhibit isoenzyme CYP2D6 at low micromolar ranges. Please refer to Appendix 3 for the list of CYP2D6 substrates. .
- Oral contraceptives are generally metabolized by CYP3A4. Since the induction potential of panobinostat to induce CYP3A4 is unknown, patients who are using oral contraceptives as a method of contraception, and are sexually active, should use another effective contraceptive method.

Anti-coagulant therapy
Panobinostat therapy is commonly associated with mild to moderate degree of thrombocytopenia. This may lead to an increase in the risk of bleeding with concomitant sodium warfarin (Coumadin®). It is recommended that patients who require anticoagulation therapy while on panobinostat therapy use low molecular weight heparin (LMWH). However, if the use of LMWH is not feasible, patients on sodium warfarin may continue such therapy while on panobinostat but for such patients, a close and frequent monitoring of the coagulation parameters, including PT/INR should be followed and they should be maintained within a therapeutic range. The dose of sodium warfarin may be adjusted as needed while on panobinostat.

8.0 CRITERIA FOR RESPONSE:

Response will be documented on tumor measurement form and/or medical record deteremined by PI per cheson criteria. Tumor measurements will be performed by radiologist

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of another nodes; (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) < 1.5 cm in any axis, ≥50% increase in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node >1cm in short axis. Lesions PET positive if FDG-avid lymphoma or PET positive prior to	>50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

		therapy.		

Cheson et al, J Clin Oncol 2007, 25:579-586

9.1 Duration of Treatment and Patient Participation

- Patients will receive 3 cycles of ICE (phase II only) or ICE + PANOBINOSTAT (LBH589) (phase I or phase II). Responding patients who are transplant eligible will be removed from the study and offered standard of care stem cell collection regimens. Non-responding patients will be offered alternative management plan by the treating physician.

9.2 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Intercurrent illness
- Occurrence of an unacceptable adverse event
- A treatment cycle delay of ICE > 14 days
- Patient request
- Protocol violations
- Non-compliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
- Progressive disease.

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

All AEs will be followed for 30 days post last dose of study drug and recorded in database

10.0 STATISTICAL CONSIDERATION:

Phase I design:

The objective of the phase I portion is to determine the maximum tolerated dose (MTD) of Panobinostat in combination with ICE. The dose level for ICE is fixed. There are three predefined dose levels for Panobinostat.

Dose Level	Panobinostat (mg, orally) Monday-Wednesday-Friday
-1	10
0	20
1	30

The standard "3+3" design will be used for the phase I portion of the trial. Dose limiting toxicity (DLT) is defined as follows: for non-hematologic toxicities, any CTCAE v4.0 Grade 3 or greater toxicity except for grade 3 fatigue, grade 3 or 4 nausea and vomiting lasting less than 72 hours after the last dose of chemotherapy, and grade 3 non-hematologic laboratory abnormalities that resolve to grade 1 or baseline (if the patient entered the study with existing toxicity) within 14 days of the first dose of ICE chemotherapy; for hematologic toxicities using CTCAE v4.0, grade 4 neutropenia lasting greater than 14 days, grade 3 febrile neutropenia requiring antibiotics, grade 4 febrile neutropenia, and Grade 4 platelet count (<25,000/mm3) at any time and lasting greater than 14 days. Applying the 3+3 design, the first cohort of 3 patients will be treated at dose level 0 and evaluated for DLT at the end of first cycle. The algorithm is as follows: (1) If 0 out of 3 patients experiences dose-limiting toxicity (DLT), the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develop a DLT, an additional 3 patients will be treated at the same dose level. If no more DLTs develop at this dose, i.e. 1 out of a total of 6 patients develops a DLT, the dose escalation continues for the next cohort of 3 patients. (3) At any given dose, if greater than 1 out 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT. Given 3 predefined dose levels, it is anticipated that up to 12 eligible patients are required for the dose-finding portion of this trial.
To better estimate the DLT rate, an expansion cohort of 10 patients will be treated at the MTD. If at any time the DLT rate exceeds 33%, then the MTD is too toxic and a lower dose than MTD will be selected for the phase II.
With the addition of Dosing Schedule B, an additional 10 patients will be treated at the MTD in a 2nd expansion cohort but at a different dosing schedule to better evaluate safety and administration of ICE.

Phase II:
The phase II part of this study is to evaluate ICE only and Panobinostat +ICE in treating patients with classical Hodgkin lymphoma. The primary outcome is complete remission (CR). The estimated accrual rate is 3 patients per month. A maximum of 70 patients will be accrued. Patients will be evaluated for response after receiving 3 doses of ICE (3 cycles). The patients will be randomized between ICE and Panobinostat + ICE arms using a Bayesian adaptive algorithm. The dose level for Panobinostat will be the dose level determined after the phase I expansion cohort. In general, the trial will proceed as follows: The initial 20 patients will be randomized fairly with probability of 0.50 each between the two arms, so that the number of patients in each arm is equal at the start of the trial. Thereafter, as the trial proceeds patients will be randomized to the two groups with unequal probabilities in favor of the treatment that, on average, yields better response rate. Consequently, each successive patient is more likely to receive the treatment with a better response rate, on average. The details of the adaptive randomization scheme are as follows:

Denote the response rate at each of the two treatment arms by $\{\pi_1, \pi_2\}$ (1 for ICE, 2 for Panobinostat+ICE). Based on the currently available data, we assume the prior distribution for the complete response rate at 3 cycles (2 months) is $\pi_i \sim$ Beta (0.5, 0.5) where i=1, 2. The resulting prior mean is 0.5. After the initial first 20 patients being randomized to two treatment groups with an equal probability, each new patient will be randomized to receive treatment i with probability ρ_i=prob($\pi_i > \pi_j$, $j \neq i$| Data), i, j=1,2. If one of these two randomization probabilities falls below 0.025 then that arm will be dropped. On the other hand, if one of the two randomization probabilities exceeds 0.975 then the trial will be terminated and that treatment arm will be selected. If the trial does not stop early and the maximum 70 patients are accrued, a treatment is selected as being "better" if the probability that one treatment's response rate is larger than the other's response rate exceeds 0.95.

The Table below summarizes operating characteristics of the Bayesian adaptive randomization algorithm after we simulated 5,000 trials. We assume that the number of patients accrue per month is 3.

		Treatment arms	
		ICE	**Panobinostat-ICE**
Scenario 1:	True Prob(Complete Remission)	0.50	0.50
	Average # Patients Treated	31.2 (10, 55)	30.8 (10, 54)
	Pr(Selected)	0.117	0.122
	Pr(Selected Early)	0.0998	0.105
	Pr(Dropped Early)	0.108	0.102
	Average Length (months) to the last patient's response evaluation	23.1	
Scenario 2:	True Prob(Complete Remission)	0.50	0.70
	Average # Patients Treated	19.1 (10, 45)	32.8 (10, 55)
	Pr(Selected)	0.0098	0.573
	Pr(Selected Early)	0.0096	0.49
	Pr(Dropped Early)	0.513	0.0096
	Average Length (months) to the last patient's response evaluation	18.8	
Scenario 3:	True Prob(Complete Remission)	0.50	0.80
	Average # Patients Treated	14.2 (10, 31)	25.7 (10, 55)
	Pr(Selected)	0.0022	0.859
	Pr(Selected Early)	0.0022	0.781
	Pr(Dropped Early)	0.808	0.0022
	Average Length (months) to the last patient's response evaluation	14	
Scenario 4:	True Prob(Complete Remission)	0.60	0.80
	Average # Patients Treated	18 (10, 42)	31.7 (10, 56)
	Pr(Selected)	0.0068	0.638
	Pr(Selected Early)	0.0068	0.556
	Pr(Dropped Early)	0.576	0.0068
	Average Length (months) to the last patient's response evaluation	17.9	

The trial will be conducted using the Clinical Trial Conduct website (https://biostatistics.mdanderson.org/ClinicalTrialConduct) developed in University of Texas MD Anderson Cancer Center Department of Biostatistics. Through the web interface, the users can randomize patients and update last evaluation date and current patient status. When a patient is randomized, the calculations are based on all available data entered into the website. The results of the randomization are displayed to the screen for the user to view. All data will be stored in a secure SQL server database.
For safety, in addition to the MDACC DSMB annual monitoring, the team including the PI, one or 2 other select investigators, and the statistician will meet at every 10 patients for the Panobinostat +ICE arm to review the toxicity data.

Analysis Plans

Patients' demographic characteristics at baseline including age, gender, and race will be analyzed, with categorical variables summarized in frequency tables while continuous variables summarized using mean (±s.d.) and median (range). The student t-test/Wilcoxon test will be used to compare continuous variables between different patient groups. The chi-square test or the Fisher's exact test will be applied to assess the association between two categorical variables. Complete remission rate along with its 95% CI will be estimated for each treatment arm. Logistic regression will be utilized to assess the effect of patient demographic factors and treatment on CR.

Time-to-event outcomes, including event-free survival (EFS), duration of response, and overall survival (OS), will be estimated using the Kaplan-Meier method. The log-rank test will be performed to test the difference in time-to-event distributions between patient groups. Cox proportional hazards model will be used to include multiple covariates in the time-to-event analysis.

Serum levels of TARC and biomarkers of interest such as HDAC1, HDAC2, pSTAT3, and pSTAT6 by IHC at baseline and change from baseline to post-treatment will be evaluated for each treatment arm. We will study the association between markers and CR using logistic regression models, and the association between markers and time-to-event outcomes using Cox proportional hazards models.

Toxicity data will be summarized by frequency tables. The association between both type and severity of toxicity and the treatment groups will be evaluated. No formal statistical testing will be performed on these summary data.

11.0 DATA AND PROTOCOL MANAGEMENT:

Data will be collected by a research nurse, and will be recorded in the PDMS Data Management System.

12.0 REPORTING REQUIREMENT of ADVERSE EVENTS

Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, vital signs, ECOG performance status, and the regular physical examinations and ECG assessments.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0. CTCAE v4.0 can be accessed on the NIH/NCI website at (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf))

For both serious and non-serious adverse events, the investigator must determine both the intensity of the event and the relationship of the event to drug administration.

Relationship to drug administration will be determined by the investigator responding yes or no to the question: Is there a reasonable possibility that the adverse event is associated with the drug?

Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 4.0, as a guideline, wherever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

All adverse events will be documented for the phase I aspect of the protocol

For the phase II aspect of the protocol; AEs will be recorded based on the Recommended AE Recording Guidelines below.

Recommended Adverse Event Recording Guidelines						
Attribution	**Grade 1**	**Grade 2**	**Grade 3**		**Grade 4**	**Grade 5**
Unrelated	Phase I	Phase I	Phase I Phase II		Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II		Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III		Phase I Phase II Phase III	Phase I Phase II Phase III

Serious Adverse Event Reporting (SAE)

Serious Adverse Event Reporting (SAE) for M. D. Anderson-Sponsored IND Protocols

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

· Death
· A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
· Inpatient hospitalization or prolongation of existing hospitalization
· A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
· 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

· Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

· All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

· All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

· Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

· Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

· Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

· Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

Pregnancies
Any pregnancy that occurs during study participation should be reported. To ensure patient safety each pregnancy must also be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities or maternal and newborn complications.

Monitoring of adverse events and period of observation

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded on the data capture records. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

IRB notification of SAE:

The following SAEs are expected events with the planned therapy, and therefore will not be reported individually to the IRB. These side effects will be collected in the PDMS system and will be summarized during the annual report, and will be reported in any future publication:

- Neutropenia
- Thrombocytopenia
- Anemia
- Nausea and vomiting
- Peripheral neuropathy
- Neutropenic fever
- Infection
- Catheter related complications including infection and thrombosis
- Electrolyte abnormalities

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APPENDIX 1: MEDICATIONS WHICH HAVE A RISK OF CAUSING TORSADES DE POINTES VENTRICULAR ARRHYTHMIA SHOULD BE AVOIDED

Patients who are currently receiving treatment of the medications in Table 1-1 and cannot either discontinue from this treatment or switch to an alternative medication prior to enrollment in a panobinostat clinical study, will be excluded from the study. Patients may not begin panobinostat treatment with any of the medications listed in Table 1-1 unless this is discussed with the Sponsor and an approval is granted by the Sponsor. The sponsor may agree to temporarily discontinue panobinostat treatment (e.g., for 72 hours) during administration with these drugs or withheld medications in Table1-1 for at least 72 hours when panobinostat is to be administered.

NOTE: It is of great importance to avoid combining drugs listed below in Table 1-1 and Table 2-1 (CYP3A inhibitors) especially in the presence of electrolyte abnormalities, notably decreased potassium or magnesium levels commonly associated with diuretic usage.

In generally, medications listed in Table 1-1 should be avoided while medications listed in Tables 2-1 and 3-1 are to be used with caution when co-administered with panobinostat. Please select the most stringent recommendation for concomitant medications (i.e., to be avoided) which are common among the tables (e.g., erythromycin, clarithromycin)

Table 0-1 Medications which have a risk of causing Torsades de pointes to be avoided

All Class IA antiarrhythmics • quinidine • procainamide • disopyramide • any other class IA antiarrhythmic drug
All Class III antiarrhythmics amiodarone sotalol bretylium disopryramide dofetilide ibutilide any other class III antiarrhythmic drug
Antibiotics Macrolide antibiotics* • erythromycin • clarithromycin • telithromycin Quinolone antibiotics* sparfloxacin
Antipsychotics thioridazine mesoridazine chlorpromazine pimozide

Antimalarials • halofantrine • chloroquine
Miscellaneous drugs • arsenic trioxide • astemizole • bepridil • domperidone • levomethadyl • methadone • pentamidine • droperidol
*Note: azithromycin, ciprofloxacin, levofloxacin, pefloxacin, ofloxacin, tosufloxacin, difloxacin, temafloxacin, fleroxacin, acrosoxacin, nalidixic acid and enoxacin are allowed.

This is not a comprehensive list of medications which may prolong the QT interval or have a risk of causing Torsades de pointes. This list of medications was developed in collaboration with an external cardiology consultant, and represents those medications which are deemed to have an unacceptable risk of co-administration with panobinostat.
The following website may be referenced as a supplemental guide for drugs which have been associated with Torsades de pointes or prolonging the QT interval but at this point lack substantial evidence for causing Torsades de pointes:
http://www.qtdrugs.org/medical-pros/drug-lists/drug-lists.htm#.
Medications listed on the website which do not appear in Table 1-1 above may be used with caution at the discretion of the investigators.
The serotonin ($5HT_3$) antagonists, often used as antiemetics, such as ondansetron dolasetron, (also are known CYP2D6 substrates, see Table 3-1), or granisetron have been associated with Torsades de points and QT prolongation but have not been shown to cause Torsades de pointes. Therefore, $5HT_3$ antagonists are not per se prohibited but close monitoring for signs and symptoms of QT prolongation is recommended. Caution is to be exercised when using these or other agents that may prolong QT intervals in combination with panobinostat.

APPENDIX 2: MEDICATIONS WHICH ARE KNOWN STRONG CYP3A4/5 INHIBITORS TO BE USED WITH CAUTION

Panobinostat is a substrate of CYP3A4 with minor involvement of CYP2D6, and CYP2C19 in *in vitro* evaluation of its metabolism. Thus, a clinical drug-drug interaction study was conducted using ketoconazole, a strong CYP3A inhibitor, in combination with panobinostat in study CLBH589B2110.

Multiple ketoconazole doses at 400 mg increased C_{max} and AUC of panobinostat by 1.6- and 1.8-fold, respectively, but with no change in T_{max} or half-lives in 14 cancer patients. The less than 2-fold increase in panobinostat AUC upon co-administration of a strong CYP3A inhibitor is considered a weak drug inhibition and not clinically relevant, as panobinostat doses at least 2-fold greater than the evaluated 20 mg dose (i.e., 40 mg and 60 mg) have been safely administered in patients. Thus, co-administration of panobinostat with a moderate or weak CYP3A inhibitor is allowed. However, clinical monitoring of signs and symptoms of panobinostat treatment related adverse events is recommended when long-term (≥ 1 week) concomitant administration of any strong CYP3A inhibitors and panobinostat is medically indicated or investigated in a clinical study.

Patients with impaired liver function (as defined by NCI CTEP criteria)[1] are recommended not to receive panobinostat concomitantly with strong CYP3A inhibitors because potential interaction has not been established in this population.

Table 2-1 Medications which are known strong CYP3A4/5 inhibitors to be used with caution

Macrolide antibiotics* • clarithromycin • telithromycin • troleandomycin • erythromycin
Antifungals (azoles)* • ketoconazole • itraconazole • fluconazole
Antidepressants • nefazodone
Calcium channel blockers* • diltiazem • verapamil
HIV protease inhibitors: • indinavir • nelfinavir • ritonavir • saquinavir
Miscellaneous drugs or products • aprepitant • grapefruit product or juice
* azithromycin, voriconazole, regular orange juice and dihydropyridine

calcium channel blockers (e.g. amlodipine, felodipine, nicardipine, nifedipine) are allowed.

This is not a comprehensive list of medications which may inhibit CYP3A4/5. Additional updated versions with moderate and weak CYP3A inhibitors, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs

APPENDIX 3: MEDICATIONS WHICH ARE KNOWN CYP2D6 SUBSTRATES TO BE USED WITH CAUTION

Panobinostat was also shown to be a CYP2D6 inhibitor (K_i 0.17 µM) *in vitro*. Thus, clinical drug-drug interaction study with panobinostat as CYP2D6 inhibitor and dextromethorpan as CYP2D6 substrate was recently conducted in study CLBH589B2109.

Multiple panobinostat doses increased C_{max} and AUC of dextromethorphan by a mean of 1.8- and 1.6-fold respectively, but with no change in T_{max} in 17 cancer patients. An approximately 2-fold increase in dextromethorphan AUC upon co-administration with panobinostat indicated that *in vivo* CYP2D6 inhibition of panobinostat is weak.

As the study was conducted using a sensitive CYP2D6 substrate which resulted in a weak inhibition, drugs with a large therapeutic index such as anti-emetics, anti-hypertensives, and anti-depressants are generally safe to be co-administered with panobinostat.

Patients should be carefully monitored for potential signs and symptoms of toxicity and may require dose titration or dose reduction of a sensitive CYP2D6 substrate which also have a narrow therapeutic window (e.g., the ratio of toxicity exposure is ≤ 2-fold higher than the efficacious or therapeutic exposure).

Table 3-1 Medications which are known CYP2D6 substrates to be used with caution

Beta blockers (listed below):	**Antipsychotics** (listed below):
carvedilol	aripiprazole
metoprolol	haloperidol
propafenone	perphenazine
timolol	risperidone
Antidepressants (listed below):	thioridazine
amitriptyline	zuclopenthixol
chlormipramine	amphetamine
desipramine	alprenolol
imipramine	bufuralol
fluoxetine	chloropheniramine
paroxetine	**Antiarrhythmics** (listed below):
venlafaxine	quinidine
bupropion	lidocaine
duloxetine	mexiletine
Antiemetics (listed below):	propafenone
dolasetron	**Others**:
ondansetron	oxycodone
metoclopramide	codeine
	hydrocodone
	terbinafine
	promethazine
	tamoxifen
	tramadol

This is not a comprehensive list of CYP2D6 substrates. Additional updated versions of this list, which are meant to be used as a guide, may be found at the following website: http://medicine.iupui.edu/clinpharm/DDIs

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