A phase I dose-escalation study of intravenous panobinostat in patients with lymphoma and solid tumors

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ABSTRACT

Purpose: Panobinostat, a pan-deacetylase inhibitor, is a promising anti-cancer agent that increases acetylation of proteins associated with growth and survival pathways of malignant cells. The primary objective of this phase I dose-escalation study was to determine the maximum tolerated dose (MTD) of intravenous (i.v.) panobinostat administered on different dosing schedules in patients with advanced solid tumors or lymphoma. Secondary objective was to characterize safety and tolerability, pharmacokinetic profiles, and activities of the i.v. formulation.

Methods: i.v. panobinostat was administered at escalating doses on a daily (days 1–3 and 8–10 of a 21-day cycle; days 1–3 and 15–17 of a 28-day cycle) or weekly (days 1, 8, and 15 of a 28-day cycle; days 1 and 8 of a 21-day cycle) schedule, and safety and tolerability were monitored. Serial blood samples were collected following dosing for pharmacokinetic and pharmacodynamic analyses.

Results: The MTD for the daily administration schedule was 7.2 g/m^2, whereas the MTD for the weekly schedule was 20.0 mg/m^2. In addition to fatigue and cardiac arrhythmias, including prolonged QTcF, DLTs associated with the study drug were principally due to myelosuppressive effects. Maximum concentrations and bioavailability of i.v. panobinostat increased dose-proportionally across all doses evaluated.

Conclusions: Based on the results of this study and others, the i.v. formulation of panobinostat was well tolerated in many patients, but concerns remain regarding its potential suitability outside the study setting due to potential electrocardiogram abnormalities. Therefore, further development will focus on the panobinostat oral formulation.

Keywords: Panobinostat, DAC, DACi, Cancer

INTRODUCTION

Acetylation, a common and reversible post-translational modification controlled by acetyltransferases and deacetylases (DACs), regulates target protein function and activity within the cell. Currently, 3600 acetylation sites on 1750 proteins have been identified in human cancer cells [1]. The balance between acetylation and deacetylation of proteins within the cell controls survival, differentiation, and cell cycle progression; thus, acetylation has emerged as a key target in cancer regulation [2]. DACs target both histones—resulting in epigenetic modifications—and non-histone proteins—including transcription factors, cellular growth factors, and molecular chaperones, leading to decreased acetylation—thereby affecting cell cycle progression and apoptosis [3]. As DACs target numerous intracellular targets, increased DAC activity within cancer cells is associated with survival of malignant cells, partly through the suppression of pro-apoptotic genes and up-regulation of anti-apoptotic genes [4, 5], disruption of cell cycle regulation [6], and stimulation of angiogenesis and cell proliferation [4, 5].

Deacetylase inhibitors (DACi) are a novel class of anti-cancer agents that target DAC enzymes and have been shown to induce growth arrest, differentiation, and apoptosis and can therefore be a useful tool in targeting malignant cells [7-10]. Panobinostat is a pan-DACi that inhibits a broad range of deacetylase enzymes (classes I, II, and IV), leading to acetylation of intracellular targets involved in oncogenesis, such as the transcription factors p53, HIF1-α, cytoskeletal factor α-tubulin, and the molecular chaperone heat shock protein 90 [11-15]. Panobinostat has been shown to inhibit proliferation and induce apoptosis in cancer cells. Although it inhibits survival of multiple tumor types, panobinostat has shown limited toxicity toward normal cells in animal models [16].

Initial clinical development of panobinostat included both oral and intravenous (i.v.) formulations. Oral panobinostat has demonstrated clinical activity in various solid tumor and hematologic malignancies and is currently being explored in myelodysplastic syndromes, myelofibrosis, and multiple myeloma phase II/III trials [17, 18]. Thrombocytopenia was identified as the primary dose-limiting toxicity (DLT) of the oral formulation but was well defined, manageable, and rapidly reversible [19]. Preliminary data in patients with refractory hematologic malignancies who received i.v. panobinostat as a 30-minute infusion on days 1–7 of a 21-day cycle demonstrated that this formulation was well tolerated at doses <11.5 mg/m^2 [20]. At higher doses (≥11.5 mg/m^2), grade 3 QTcF prolongation was observed but was asymptomatic and reversible upon drug discontinuation. However, a relationship between QTcF and plasma pharmacokinetic variables (maximum plasma drug concentration [C_{max}] and area under the concentration–time curve from time 0 to 24 hours [$AUC_{0–24h}$]) was not observed, and it was suggested that panobinostat was prolonging QTcF but that it was not time dependent on the C_{max} or AUC. A consecutive 7-day dosing schedule was chosen to maintain drug efficacy over an extended period of time to maximize drug exposure for patients with leukemia, but this schedule was not considered feasible for future i.v. studies.

The current study expands on the panobinostat dosing strategies and investigates alternatives to the dosing schedule used in the prior i.v. study in an attempt to reduce toxicities and improve efficacy. Given the activity seen across multiple indications, it is necessary to further develop these initial observations regarding the i.v. formulation and identify an effective and tolerable dosing regimen and schedule for i.v. panobinostat in a broad patient population. This phase I study in patients with solid tumors and lymphomas attempted to determine the maximum tolerated dose (MTD), DLT, and safety profile of i.v. panobinostat.

MATERIALS AND METHODS

Patient selection

This study adhered to the Declaration of Helsinki and the International Conference on Harmonisation ICH Harmonised Tripartite Guidelines for Good Clinical Practice. Approval was obtained from a number of independent ethics committees and local institutional review boards. All patients provided written, informed consent.

Patients aged ≥18 years with advanced solid tumors who had progressed on standard therapies or who were no longer receiving standard therapies, or those with relapsed or refractory Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) who were not considered appropriate candidates for standard therapy, were eligible for this study. Eligibility criteria also included a World Health Organization (WHO) performance status ≤2; neutrophil count ≥1.5 × 10^9/L; hemoglobin ≥9 g/dL; platelets ≥75 × 10^9/L (<75 to 50 × 10^9/L if thrombocytopenia was related to progressive HL or NHL with bone marrow infiltration); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤2.5 × upper limit of normal (ULN), or AST and ALT ≤5.0 × ULN in patients with liver metastases; serum bilirubin ≤1.5 × ULN; serum creatinine ≤1.5 × ULN; or 24-hour clearance ≥50 mL/min. Patients with Common Terminology Criteria for Adverse Events (CTCAE) ≥grade 2 peripheral neuropathy or those with hepatic or renal disease were not eligible. Due to the possible effects of DACi leading to QT prolongation, patients with impaired cardiac function or those at risk of torsades de pointes were not eligible. Prior treatment-related exclusions included bone marrow or stem cell transplant within 4 months of study; chemotherapy, investigational drug, or wide-field radiotherapy ≤4 weeks prior to study; immunotherapy, major surgery, treatment with hematopoietic colony-stimulating growth factors, or palliative limited-field radiation ≤2 weeks prior to starting study drug; and concomitant use of CYP3A4/5 medications.

Study design and drug administration

There were 2 phases to this study: the dose-escalation phase and the dose-expansion phase. This study consisted of 4 arms with varying doses and schedules for i.v. panobinostat (Fig.). Panobinostat

was administered by 30-minute i.v. infusions at approximately the same time during each day of dosing. The infusion was stopped if the patient experienced any cardiovascular toxicity ≥CTCAE grade 2, any toxicity ≥CTCAE grade 3, or any other clinically significant toxicity.

Following completion of cycle 1, patients received subsequent cycles of panobinostat based on the absence of unacceptable toxicity and/or disease progression. A modified accelerated titration design was used for dose-level selection and determination of MTD in patients in treatment Arms 1 and 2 [21]. During treatment cycle 1, each treatment arm independently enrolled a series of single-patient cohorts, with dose doubling between each cohort until the second occurrence of a ≥CTCAE grade 2 toxicity or the first occurrence of a worse toxicity. At that time, the current cohort and all future cohorts were expanded to enroll 3 to 6 patients. When a DLT was encountered, a maximum of 3 more patients were treated at that same level. When a minimum of 2 patients experienced a DLT at a given dose, this dose was considered to have exceeded the MTD.

For determination of the treatment Arm 3 starting dose, a 2-parameter Bayesian logistic regression model [22] incorporated all of the toxicity data obtained from treatment Arms 1 and 2, including available DLT data, in order to predict the MTD, defined as the dose resulting in a targeted DLT rate of 20% to 35%. The model was re-evaluated at any time if 2 patients in a cohort experienced a DLT. The dose-escalation phase ended when 6 evaluable patients had been enrolled at the MTD and at least 24 patients had been enrolled in total.

The dose-escalation model was evaluated for treatment Arm 4, while a starting dose was based on the safety profile observed for Arm 3. The MTD-evaluable patient population included only patients who met the minimum safety evaluation requirements of the study. These requirements include receiving 2 consecutive doses of panobinostat within a 3-week period during cycle 1, completing all required safety evaluations, and undergoing observation for ≥7 days following the last of the 2 weekly doses of panobinostat in the treatment cycle. A patient who experienced a DLT in cycle 1 of therapy was also evaluable, regardless of the number of doses given or the amount of follow-up. The model was re-evaluated if 2 patients in a cohort experienced a DLT before the sixth patient in the cohort became evaluable, or if 3 patients in a cohort experienced a DLT before the ninth patient in the cohort became evaluable. Only 3 patients were initially allowed to enroll in the first dose cohort in Arm 4; no additional patients were allowed to begin treatment until each of the first 3 patients had completed 1 cycle of treatment and their electrocardiogram (ECG) data had been evaluated.

Safety and efficacy

Patients were monitored throughout the trial with regular laboratory and cardiac evaluations, and all adverse events (AEs) and serious adverse events (SAEs) were recorded according to CTCAE version 3.0. Patients with HL and NHL had serum lactate dehydrogenase determinations performed at baseline and at the time that complete response (CR) or CR unconfirmed (with the exception of bone scan

abnormalities) was documented. Cardiac assessments included ECGs for QTc interval observation, multi-gated acquisition angiography scan, or echocardiogram to assess left ventricular ejection fraction.

Efficacy was assessed by radiological and physical exams. Computed tomography scans (or magnetic resonance imaging) were scheduled at baseline and at the end of every other cycle while patients were treated with panobinostat. Response was assessed by modified standard Response Evaluation Criteria In Solid Tumors (RECIST) endpoints for advanced solid tumors; Cheson criteria were used for patients with HL or NHL, and physician's global assessment (PGA) and composite assessment were used for patients with cutaneous T-cell lymphoma (CTCL) [23-27]. The determination of response required confirmation after at least 4 weeks. Disease progression was based on objective evidence documented by radiological study or physical examination.

Pharmacokinetic analysis

Blood samples were collected to characterize the pharmacokinetics (PK) of panobinostat in patients during both the dose-escalation and dose-expansion phases of the study. Serial whole blood samples (3 mL) were collected in tubes containing sodium heparin at specified time points. Immediately after collection, tubes were inverted several times and kept at approximately 4°C until centrifugation. The tubes were centrifuged for 15 minutes at 800 × g at 4°C within 60 minutes of collection to separate plasma. The plasma was separated into 2 aliquots (of at least 1 mL each) in polypropylene screw-cap tubes and placed at −60°C until analysis.

Blood samples from patients in treatment Arms 1 and 2 were collected during cycle 1, day 1 at the following time points: 0 (prior to drug administration), 0.25, 0.5 (immediately before stopping infusion), 0.583 (35 minutes, exactly 5 minutes after stopping infusion), 0.75, 1, 2, 4, 6, 8, and 24 hours post dose. Cycle 1, day 3 time points were the same as for cycle 1, day 1 but with additional samples collected at 10 and 48 hours post dose. Blood samples from patients in treatment Arms 3 and 4 were collected during cycle 1, days 1 and 8 at the following time points: 0 (prior to drug administration), 0.25, 0.5 (immediately before stopping infusion), 0.583 (35 minutes, exactly 5 minutes after stopping infusion), 0.75, 1, 2, 4, 6, 8, 24, and 48 hours post dose.

Plasma samples were analyzed for panobinostat concentrations by a validated liquid chromatography–tandem mass spectrometry method with a lower limit of quantification (LLOQ) of 0.5 ng/mL. The assay has a dynamic range of 0.5 to 500 ng/mL using a 0.1-mL sample volume [28].

Pharmacodynamic analysis

Whole blood samples (8 mL) were collected and analyzed for acetylation of histones H3 and H4 to assess the pharmacodynamic effects of panobinostat administration, and were analyzed for histone acetylation by Western blot analysis. A positive reading was defined as a >2-fold increase in H3 or H4

acetylation compared with baseline as detected by Western blot. Positivity was based on a previous observation demonstrating that a two-fold increase in H3 acetylation in peripheral blood mononuclear cells (PMBCs) as detected by Western blot correlated with intratumoral acetylation in cutaneous T-cell lymphoma patients treated with panobinostat [29]. Blood samples from patients in treatment Arms 1 and 2 were collected during cycle 1, day 1 at the following time points: 0 (prior to drug administration), 1, 3, and 6 hours post-dose. Cycle 1, day 3 time points were the same as for cycle 1, day 1. Subsequent samples were taken pre-dose (0 hour) on days 4, 8, and 15. Blood samples from patients in treatment Arms 3 and 4 were collected during cycle 1, days 1 and 8 at the following time points: 0 (prior to drug administration), 1, 3, and 6 hours post-dose. Subsequent samples were taken pre-dose (0 hour) on days 9 and 15.

Statistical methods

Data from all participating centers were combined to achieve adequate patient numbers for analysis. In treatment Arms 1 and 2, a modified accelerated titration design was used for selection of the dose and determination of MTD [21]. In treatment Arms 3 and 4, dose selection for each cohort of new patients was done adaptively using a 2-parameter logistic model for the probabilities of DLT [30].

All patients receiving at least one dose of medication and one post-baseline safety assessment were included in the safety analysis set, and those who met the minimum safety evaluation requirements were included in the MTD-determining set. The assessment of safety was based mainly on the frequency of AEs (CTCAE v.3.0) and on the number of laboratory values that fell outside pre-determined ranges as outlined in the protocol. ECG abnormalities were also monitored. The rate of best overall response was based on the modified RECIST for patients with solid tumors, on modified Cheson criteria for patients with HL and NHL, and on the PGA for patients with CTCL [23-27].

Statistical analyses were performed for the following PK parameters: C_{max}, area under the concentration–time curve from time zero to infinity ($AUC_{0-\infty}$), total body clearance, volume of distribution, and terminal half-life ($t_{1/2}$). These analyses included determination of the mean, standard deviation, coefficient of variation, and geometric mean. Individual panobinostat plasma concentration–time curve following each dose was used to calculate PK parameters using non-compartmental methods, as implemented in WinNonlin® Pro software (Version 5.01, Pharsight Corporation, Mountain View, CA, USA). Patients with at least one evaluable PK profile were included in the PK data analysis, and calculation of PK parameters included concentrations only up to the last measurable concentration (ie, above the LLOQ). C_{max} values >2000 ng/mL were not summarized, as those values are associated with bolus injection rather than infusion. C_{max} and time to maximum plasma drug concentration (T_{max}) were obtained by visual inspection of the concentration–time curve. $AUC_{0-\infty}$ was calculated using a linear up/log down method up to the last measured concentrations, the additional area estimated from that concentration, and the $t_{1/2}$ estimated for the targeted administration. Estimation of $t_{1/2}$ was conducted using the best-fit

variables of a single exponential to the log-linear portion of the plasma concentration–time curve by non-weighted linear regression.

RESULTS

Patient demographics and characteristics

Demographic characteristics were similar across all treatment arms (Table 1). Age ranged from 33 to 83 years. Mean body surface area was between 1.9 and 2.0 m^2 for each parameter across each treatment arm. WHO performance status (PS) was also comparable across the 4 arms, with the majority of patients (67.4) having a PS of 1. More males than females were enrolled in each treatment arm, and the majority of patients (87%) in the study were white.

All patients enrolled in Arms 1, 2, and 4 had a diagnosis of solid tumors. In Arm 3, 1 patient was diagnosed with NHL, 4 with CTCL, 3 with peripheral T-cell lymphoma (PTCL), and 39 with solid tumors. A substantial proportion of patients experienced their most recent relapse/recurrence within 3 months prior to enrollment: 35% of patients in Arm 1, 57% in Arm 2, 23% in Arm 3, and 78% in Arm 4. Many patients did not respond to the most recent prior medication regimen, with 61% in Arm 1, 40% in Arm 3, and 33% in Arm 4 achieving a best response of progressive disease (PD).

Patient disposition

All patients enrolled in the study discontinued. Of the 23 patients in Arm 1, 16 discontinued due to disease progression, 4 withdrew consent, 2 discontinued due to AEs, and 1 discontinued due to increased liver enzyme values. Overall median exposure was 42 days (range, 8–399 days).

Of the 7 patients in Arm 2, 3 patients discontinued the study due to disease progression, 2 withdrew consent, and 2 discontinued due to AEs. Overall median exposure was 56 days (range, 15–267 days).

Of the 47 patients enrolled in Arm 3, 28 discontinued due to disease progression, 5 withdrew consent, 7 discontinued due to AEs, 4 discontinued for other protocol-mandated reasons, and 3 discontinued due to unsatisfactory therapeutic effects (lack of disease response from the agent to warrant continuation of therapy, as determined by the investigator). Overall median exposure was 56 days (range, 8–629 days).

Of the 9 patients in Arm 4, 3 patients discontinued due to disease progression and 6 patients discontinued due to AEs. Overall median exposure was 21 days (range, 8–252 days) and median duration of exposure decreased with increasing dose.

A total of 13 deaths was reported. Eight deaths occurred on study during study treatment or during the 28-day follow-up period, while 5 occurred off study. Eleven of the 13 patients died due to study indication (kidney cancer [n=2], prostate cancer [n=2], and 1 of each of the following: colon cancer, esophageal cancer, lung cancer, pancreatic cancer, peritoneal cancer, pleural cancer, and thyroid

cancer),and 2 patients died due to AEs not attributed to study drug (pneumonia and sepsis). Although none of the deaths was attributed to study drug, the potential role of myelosuppression was examined in conjunction with the 2 deaths due to AEs. Both of these patients were treated in Arm 3 in the same 20.0 mg/m^2 dose cohort. The patient with pneumonia had no signs of overt myelosuppression, and the death does not appear to have had a relationship to the myelosuppressive effects of panobinostat. The patient who died of sepsis, however, reported grade 4 neutropenia on study day 41 (5 days prior to death) and grade 3 thrombocytopenia on study day 43 (3 days prior to death). Both the neutropenia and thrombocytopenia events were reported as having a suspected relationship to study drug.

Determination of MTD

The evaluable patient set for determination of MTD (22 patients in Arm 1, 6 in Arm 2, 19 in Arm 3, and 8 in Arm 4) consisted of patients who met the minimum safety and dosing requirements or had a DLT during cycle 1. Determination of MTD and details of DLTs are summarized in Table 2.

For daily i.v. administration of panobinostat in Arm 1 (days 1–3 and 8–10 of a 21-day cycle), 7.2 g/m^2 was defined as the MTD. No DLTs were reported at the 1.2 mg/m^2 or 2.4 mg/m^2 dose. At the 4.8 mg/m^2 dose, 1 of the 3 evaluable patients experienced grade 3 neutropenia that was initially reported as a DLT but was later determined as not meeting the protocol-defined DLT criteria. At the 7.2 mg/m^2 dose, 1 of 6 evaluable patients experienced a DLT (grade 2 thrombocytopenia). At the 9.0 mg/m^2 dose, 5 of 8 patients experienced 1 or more DLTs, including grade 4 thrombocytopenia (3 patients), grade 3 neutropenia (1 patient), grade 4 neutropenia (1 patient), and grade 3 hyperbilirubinemia (1 patient). Due to the increased occurrence of myelosuppression, 9.0 mg/m^2 was determined to be excessively toxic for the Arm 1 dose schedule.

No significant toxicity was observed at the 2.4, 4.8, or 9.6 mg/m^2 dose in Arm 2 (days 1–3 and 15–17 of a 28-day cycle). A single patient, treated at the 20.0 mg/m^2 dose, experienced a DLT, a 13-beat episode of torsades de pointes occurring 36 hours after the second panobinostat dose. Additional AEs reported for this patient included prolonged QT interval, grade 3 sinus bradycardia, grade 4 neutropenia, grade 3 thrombocytopenia, grade 2 anemia, and grade 3 transaminitis. It was the judgment of the treating physicians that the hematologic toxicity and transaminitis were related to panobinostat administration, and that a contribution of panobinostat to the cardiac events could not be ruled out. Therefore, due to cardiac safety concerns, enrollment to the consecutive daily dosing schedule was completed at the decreased dose of 15.0 mg/m^2 and eventually discontinued in favor of a weekly schedule for the subsequent treatment arm (Arm 3). A formal MTD was not defined for Arm 2.

A 2-parameter Bayesian logistic regression model was used to determine the Arm 3 starting dose and incorporated the toxicity data obtained from Arms 1 and 2, including available DLT data. For Arm 3 (days 1, 8, and 15 of a 28-day cycle), no DLTs were observed at the 10.0 or 15.0 mg/m^2 dose. A single DLT (grade 4 thrombocytopenia) was reported for 1 patient at 20.0 mg/m^2. This dose was considered the

potential MTD and was expanded to evaluate an additional 23 patients to further evaluate the safety and tolerability. This dose was deemed tolerable; and due to concern about the potential for AEs at higher doses, further dose escalation was not conducted for this schedule, and 20.0 mg/m^2 was declared the MTD.

Patients in Arm 4 (days 1 and 8 of a 21-day cycle) received a starting dose of 25.0 mg/m^2; following treatment of 3 patients, 2 were evaluable, with 1 experiencing a DLT (grade 3 fatigue). It was decided that this dose was not well tolerated due to excessive fatigue, cytopenia, and electrolyte abnormalities, so no additional patients were treated at this dose. Subsequently, a 20.0 mg/m^2 cohort was opened to accrual; 6 patients were treated at the reduced dose, and each met the criteria for inclusion in the MTD-determining set. Although the MTD was not formally determined in this arm, it was decided that 20.0 mg/m^2 administered on days 1 and 8 of a 21-day cycle could be safely administered.

In general, the DLTs that occurred in study Arms 1 and 3 were principally due to the myelosuppressive effects of panobinostat, particularly thrombocytopenia (ranging from grade 2 to grade 4). The MTDs defined for Arm 1 (a daily dosing schedule) and Arm 3 (a weekly dosing schedule) were 7.2 mg/m^2 and 20.0 mg/m^2, respectively. MTD was not determined in Arms 2 and 4 due to safety issues and DLTs experienced by patients; therefore, further detailed data on safety and efficacy will not be presented for these dosing schedules.

Safety

Safety data for patients treated in Arms 1 and 3 are shown in Tables 3 and 4. The incidence of AEs and discontinuations due to AEs was generally dose dependent. Thirteen (57%) of the 23 patients in Arm 1 had a grade 3 or 4 AE considered related to study drug, while the incidence among the 43 patients in Arm 3 was 51%. Only 1 (4%) of 23 patients in Arm 1 discontinued due to AEs related to the study drug (7.2 mg/m^2 dose, grade 3 increased ALT), as did 3 (6%) of 47 patients in Arm 3 (10.0 mg/m^2 dose, grade 2 hyperbilirubinemia; 20.0 mg/m^2 dose, grade 2 fatigue, grade 2 general physical health). Grade 3/4 AEs that occurred at each dose level are shown in Table 4. Overall, thrombocytopenia was the most common grade 3/4 AE observed (n=27, 39%), reported by 8 of 23 patients (35%) in Arm 1 and 19 of 47 patients (40%) in Arm 3. Fatigue (n=10, 14%) and anemia (n=9, 13%) were also common, with more patient events observed in Arm 3 (9 and 7 patients, respectively) than at the lower doses administered in Arm 1.

SAEs were observed in a total of 9 patients (39%) in Arm 1, 4 of whom were in the 9.0 mg/m^2 cohort. Likewise, 31 patients (66%) in Arm 3 reported SAEs, 22 of whom were in the 20.0 mg/m^2 cohort. Thrombocytopenia was the most frequent SAE reported in both arms. There was 1 death reported in Arm 1 (9.0 mg/m^2 cohort) and 9 deaths in Arm 3 (1 in 10.0 mg/m^2 cohort; 2 in 15.0 mg/m^2 cohort; and 6 in 20.0 mg/m^2 cohort).

Several cardiac events requiring dose adjustment or study drug interruption were observed in patients in this study. In Arm 1 at 9.0 mg/m^2, there were 4 patients with T-wave inversion, 1 patient with a

maximum QTcF >500 ms, and 1 patient with a >60-ms change from QTcF baseline. Cardiac events occurring in >10% of patients were not observed in this arm. In Arm 2, there were 2 patients with ST-segment depression (15.0 mg/m^2 and 20.0 mg/m^2), 2 patients with T-wave amplitude decrease (15.0 mg/m^2 and 20.0 mg/m^2), 1 patient with a maximum QTcF >500 ms (20.0 mg/m^2), and 1 patient with a >60-ms change from QTcF baseline (20.0 mg/m^2). In Arm 3 at 20.0 mg/m^2, there were 12 patients with ST-segment depression, 8 patients with biphasic T waves, 6 patients with T-wave inversion, 1 patient with a maximum QTcF >500 ms, and 3 patients with a >60-ms change from QTcF baseline. In Arm 3 at 10.0 mg/m^2 and 15.0 mg/m^2, there were 5 patients with ST-segment depression (1 in 10.0 mg/m^2 cohort and 4 in 15.0 mg/m^2 cohort), 2 patients with T-wave inversion (1 in 10.0 mg/m^2 cohort and 1 in 15.0 mg/m^2 cohort), and 1 patient with biphasic T waves (15.0 mg/m^2). In this arm, there was a >10% incidence of hypotension in the 2 higher-dose cohorts (15.0 and 20.0 mg/m^2) as well as transient study drug infusion–associated mild hypotension. In Arm 4 at 20.0 mg/m^2, there was 1 patient with a maximum QTcF >500 ms, 1 patient with a >60-ms change from QTcF baseline, 3 patients with biphasic ST waves, and 3 patients with T-wave inversion. In Arm 4 at 25.0 mg/m^2, there was 1 patient with a >60-ms change from QTcF baseline and 1 patient with T-wave inversion.

Dose-limiting cardiac toxicities leading to discontinuation of study drug included grade 3 sinus bradycardia and grade 4 torsades de pointes in 1 patient in Arm 2 (20.0 mg/m^2) and 1 patient with grade 3 prolonged QTc in Arm 4 (20.0 mg/m^2). The torsades de pointes was transient and did not cause any hemodynamic compromise. Additionally, this patient had significant co-morbidities, including prolonged QTc at baseline, hypokalemia, and bradycardia. This event was also complicated by the co-administration of citalopram and hydrocodone, medications known to be associated with QTc prolongation. There was an additional patient in Arm 2 who discontinued due to grade 1 left bundle-branch block.

Pharmacokinetics

Panobinostat PK parameters for the 1.2 to 20.0 mg/m^2 doses with adequate sample size are depicted in Table 5. The mean $t_{1/2}$ of panobinostat ranged from 15 to 17 hours following a single dose, with the last available sampling time at least 36 hours post dose. Typically, a sampling time of at least 3 times as long as the half-life is required to adequately determine the $t_{1/2}$; thus, the $t_{1/2}$ obtained from the daily schedules (Arm 1) was most likely underestimated. Similarly, half-lives obtained on day 3 for Arm 1 (21.8 h for 7.2 mg/m^2 and 30.2 h for 9.0 mg/m^2) were slightly higher than those obtained on day 1 (9.8 h for 7.2 mg/m^2 and 9.1 h for 9.0 mg/m^2) due to a longer sampling time on day 3. In general, half-lives obtained on day 8 following the weekly schedule (Arm 3) were comparable after a single dose and were independent of the dose, while panobinostat C_{max} and AUC increased dose-proportionally following a single dose. C_{max} at the 20.0 mg/m^2 MTD was 783.5 ng/mL. The accumulation ratio of panobinostat was calculated as the ratio of $AUC_{0–24h}$ on day 3 to day 1 in Arms 1 and 2 and the ratio of the area under the concentration–time curve from time 0 to 48 hours ($AUC_{0–48h}$) on day 8 to day 1 in Arm 3. In Arm 1, an

approximate 40% increase in AUC was observed on day 3 compared with day 1. Drug accumulation was observed with the daily dose schedule (Arm 1) but not with the weekly dose schedule (Arm 3).

DAC inhibition

Histone acetylation (Table 6) was measured in peripheral blood mononuclear cells (PMBCs) and served as a means for identification of patients in which the biological activity of panobinostat had potentially been demonstrated. Panobinostat induced histone acetylation in most patients, even at the lower doses of 4.8 and 7.2 mg/m^2. A positive reading, defined as a >2-fold increase in histone acetylation compared with baseline, was seen for at least one time point in 100% of patients beginning at the 9.0 mg/m^2 dose through the 20.0 mg/m^2 dose. For patient samples from Arm 1, acetylation was maintained up to cycle 1 day 8 for nearly all patients analyzed (Supplementary Table 1). For Arm 3, which used less frequent dosing of panobinostat, histone acetylation was observed in > 90% of patients for time points taken 1, 3, and 6 hours postdose; however, acetylation was observed at lower levels (42.3-85.3%) at all predose time points (Supplementary Table 2). Panobinostat demonstrated measurable biologic activity at and even well below the MTD (20.0 mg/m^2).

Efficacy

Efficacy data were reported for 23 evaluable patients in Arm 1 and 47 evaluable patients in Arm 3. Overall, only 3 (4.3%) of the total 70 evaluable patients experienced a partial response (PR), and all 3 of those patients were in Arm 3. There were 2 PRs in the 15.0 mg/m^2 dose cohort (a patient with stage IV PTCL and a patient with stage I CTCL) and 1 in the 20.0 mg/m^2 cohort (a patient with Gleason grade 9 stage IV prostate cancer). Stable disease was observed in 25 (35.7%) patients and 24 (34.3%) demonstrated PD. Status was unknown for 19 (27.1%) patients, 10 of whom did not have an end-of-treatment assessment. In Arm 1, 5 (21.7%) patients, one in each dose cohort, experienced stable disease, 11 (47.8%) patients had PD, and the status was unknown for the remaining 7 (30.4%) patients. In Arm 3, 19 (40.4%) experienced stable disease, 13 (27.7%) patients had PD, and the status was unknown for the remaining 12 (25.5%) patients.

DISCUSSION

This phase I dose-escalation and -expansion study explored various doses and schedules to determine the MTD of i.v. panobinostat. The secondary objective was to characterize safety and tolerability, PK, and anti-tumor activity of the i.v. formulation. This study was originally designed to enroll patients into escalating dose cohorts and expand at the MTD to further explore safety and efficacy, but due to safety concerns the MTD was formally determined in Arms 1 and 3 only. The MTD declared for

Arm 1, in which low doses were administered on a daily schedule, was 7.2 mg/m^2; and for Arm 3, in which higher doses were administered on a weekly schedule, the MTD was 20.0 mg/m^2. A majority of DLTs were related to myelosuppression, thrombocytopenia, and neutropenia. Other nonhematologic DLTs included fatigue and cardiac abnormalities. DLTs associated with the 20.0 mg/m^2 MTD included grade 3 fatigue and grade 3 QTcF prolongation.

Panobinostat concentrations and AUC increased dose-proportionally up to 20.0 mg/m^2, and drug accumulation was observed with the daily dose schedule but not with the weekly dose schedule. The PK of i.v. panobinostat followed a linear process. In addition, the C_{max} for the 20.0 mg/m^2 dose was 783.5 ng/mL, which was approximately 30 times higher than the C_{max} of oral panobinostat. At higher doses of the oral formulation, toxicities were observed without an increase in PK (manuscript in preparation). It is hypothesized that a higher C_{max} from the i.v. formulation, and presumably drug accumulation observed with the daily dose schedule (Arm 1), may have contributed to the higher toxicities observed in the i.v. study.

QTc prolongation is a known DACi class effect that has been shown to be manageable through modifying dosing schedules and monitoring in clinical studies [31-37]. The potential for panobinostat-related QTc prolongation was supported by in vitro hERG channel inhibition (half maximal inhibitory concentration [IC_{50}] of 3.9 µM) [20]. In a previous study evaluating a consecutive 7-day dosing schedule of i.v. panobinostat, grade 3 QTcF prolongation was observed in 3 of 5 patients at the highest dose (14.0 mg/m^2) [20]. Interestingly, the mean C_{max} observed in patients treated at 14.0 mg/m^2 was 556.6 ng/mL (standard deviation [SD]±450.9) or ≈1.6 µM (SD range, 0.3–2.9 µM), which approached the in vitro hERG channel IC_{50} value. Therefore, in the current study, dose and schedule modifications were explored. Cardiac events (torsades de pointes and QTc prolongation [Table 2]) were observed in patients who received 20.0 mg/m^2 of i.v. panobinostat (mean C_{max} of 783.5 ng/mL, SD±350.20 [≈2.24 µM; SD range, 1.24–3.24 µM]). Combined, these data suggest that the increased C_{max} associated with i.v. panobinostat could lead to increased risk of QTc prolongation. Conversely, in a study of oral panobinostat (N = 36), the mean C_{max} of the MTD (20 mg) was 23.6 ng/mL (≈0.068 µM), which was approximately 55-fold less than the hERG channel IC_{50} (unpublished data). Furthermore, in a comprehensive study of pooled safety data from 554 patients treated with oral panobinostat (23,017 individual ECG measurements), grade 3/4 QTcF events (>500 ms) were observed in only 1.4% of patients treated at any dose and in <1% of patients treated with up to 45 mg [38]. Taken together, these data support the development of the oral formulation of panobinostat, which has a low incidence of QTc prolongation.

As a result of the prior i.v. study's safety profiles and the investigators' concerns in this study regarding cardiac toxicities during the daily schedules at higher dose levels, consecutive daily i.v. dosing was ultimately abandoned and a 2-parameter Bayesian logistic regression model was developed to guide dose level selection and predict the MTD beginning with study Arm 3. Arm 3 proceeded at a starting dose of 10.0 mg/m^2 administered on days 1, 8, and 15 of a 28-day treatment cycle based on an analysis of safety and PK data from Arms 1 and 2. DLTs were not observed at 10.0 mg/m^2 or 15.0 mg/m^2. However,

among the 6 evaluable patients treated at the 20.0 mg/m^2 dose, a DLT of grade 4 thrombocytopenia was observed in 1 patient. This dose level was considered the potential MTD and is the dose recommended for further evaluation. An additional 23 patients were enrolled to further evaluate the safety and tolerability profile of panobinostat when administered at this dose and schedule. Following evaluation of this cohort, further dose escalation was not conducted due to investigators' concern about the overall incidence of thrombocytopenia and fatigue. AEs related to i.v. panobinostat administered at this dose and schedule included fatigue, decreased appetite, vomiting, dehydration, nausea, increased blood creatinine, hypomagnesemia, and thrombocytopenia. Weekly i.v. dosing provided a notably improved risk/benefit profile compared with daily dosing regimens.

Preliminary anti-tumor activity was seen in 3 patients in Arm 3: 1 patient with metastatic prostate cancer (20.0 mg/m^2), 1 patient with PTCL (15.0 mg/m^2), and 1 patient with CTCL (15.0 mg/m^2). Histone acetylation response served as a surrogate measure of panobinostat activity and suggested a trend for panobinostat-associated biologic activity at or below the 20.0 mg/m^2 dose. Panobinostat-induced histone acetylation was observed in most patients, even at the lower doses, and 100% of patients who received a dose ≥9.0 mg/m^2 had a positive acetylation reading. Acetylation was observed in a high percentage of patients in nearly all time points analyzed in Arm 1, including the predose time points on days 3, 4, and 8. For Arm 3, while acetylation was observed in a majority of patient samples collected postdose on the days of panobinostat dosing, acetylation was observed in a lower percentage of patients at all predose time points. Although relatively small patient numbers were evaluated, these data suggest that more frequent dosing of intravenous panobinostat is necessary to maintain acetylation within PMBCs of patients. Due to the lack of efficacy observed in this study, firm conclusions of an association between acetylation and response could not be determined. A previous study evaluating the oral formulation of panobinostat in patients with CTCL demonstrated that responding patients displayed H3 acetylation within PMBCs and tumors [29]. In addition, that study demonstrated that panobinostat alters intratumoral expression of genes that regulate apoptosis, immune regulation, and angiogenesis [29]. Histone acetylation at 24 hours has been shown to correlate with response in patients with PTCL and CTCL patients treated with the DACi romidepsin [39]. Future studies should examine the relationship between histone acetylation as well as other novel biomarkers and efficacy in larger studies conducted of patients with indications that are associated with response to single-agent panobinostat.

During the development of novel agents used in the treatment of cancer, it is critical to identify not only the dose and schedule but often the optimal formulation. Several factors, including efficacy, safety, PK/PD, and ease of administration, are critical in determining the path forward in drug development. Although the i.v. formulation of panobinostat was well tolerated by many patients treated on this trial, the potential for QTc prolongation with daily dosing may limit the utility of this formulation outside the clinical trial setting. Therefore, the decision has been made not to pursue further development of the i.v. formulation of this drug and instead focus on the oral formulation. This decision is supported by recent

data on the oral formulation demonstrating clinical activity in various malignancies along with well-defined, manageable, and reversible toxicities [17, 18].

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CONFLICT OF INTEREST DISCLOSURES

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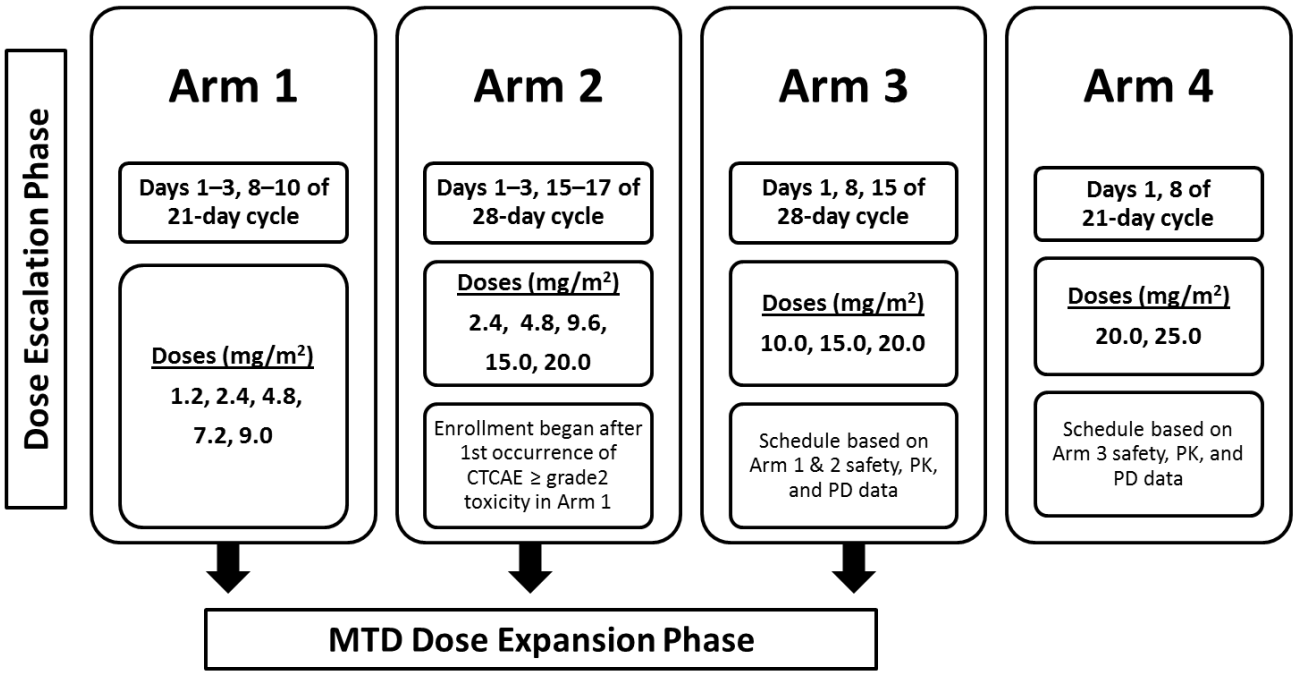
FIGURE LEGEND

Figure 1.

Patients with advanced solid tumors and NHL, including CTCL, who progressed despite standard therapy or for whom no standard therapy exists were administered intravenous panobinostat for 30 minutes once daily on specified days for each treatment arm. Each arm signifies a different schedule at various increasing doses. Panobinostat was administered in Arm 1 at a 1.2 mg/m^2/day starting dose on days 1–3 and 8–10 of a 21-day cycle. In Arm 2, panobinostat was administered on days 1–3 and 15–17 of a 28-day cycle at a starting dose based on the dose at which the first ≥CTCAE grade 2 toxicity occurred in Arm 1 (2.4 mg/m^2). Panobinostat was administered in Arm 3 at a starting dose (10.0 mg/m^2) based on an analysis of safety and PD data obtained from Arms 1 and 2 using a 2-parameter Bayesian logistic regression model [22], on days 1, 8, and 15 of a 28-day cycle. For Arms 1 through 3, additional patients (total=20) were enrolled and treated at the MTD once it was defined for a treatment arm. In Arm 4, panobinostat was administered at a starting dose based on the safety profile observed for Arm 3, on days 1 and 8 of a 21-day cycle. Only 3 patients were initially allowed to enroll in the first dose cohort in Arm 4; no additional patients were allowed to begin treatment until each of the first 3 patients had completed 1 cycle of treatment, and dose escalation was to end in Arm 4 when 10 evaluable patients had been enrolled at the recommended MTD. The initial dose of 25.0 mg/m^2 was to be administered to 10 patients; however, due to DLTs observed in the first 3 patients treated at this dose, the dose was reduced to 20.0 mg/m^2. CTCAE, Common Terminology Criteria for Adverse Events; CTCL, cutaneous T-cell lymphoma; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; NHL, non-Hodgkin lymphoma; PD, pharmacodynamics; PK, pharmacokinetics

FIGURE

Fig 1. Study design for intravenous panobinostat dose escalation and expansion



TABLES

Table 1. Patient demographics and characteristics

Demographic Characteristics	Study Arm				
	Arm 1 (n=23)	Arm 2 (n=7)	Arm 3 (n=47)	Arm 4 (n=9)	Total (N=86)
Male gender, n (%)	15 (65.2)	4 (57.1)	33 (70.2)	4 (44.4)	56 (65.1)
Age, mean (range), years	59.9 (45–79)	64.1 (51–75)	62.1 (33–83)	65.2 (51–76)	62.0 (33–83)
BSA, mean (range) m^2	1.9 (1.5–2.4)	1.9 (1.7–2.2)	2.0 (1.5–3.0)	2.0 (1.5–2.6)	2.0 (1.5–3.0)
WHO performance status, n (%)					
0	5 (21.7)	2 (28.6)	13 (27.7)	1 (11.1)	21 (24.4)
1	17 (73.9)	3 (42.9)	31 (66.0)	7 (77.8)	58 (67.4)
2	1 (4.3)	2 (28.6)	3 (6.4)	1 (11.1)	7 (8.1)
Disease type, n (%)					
Prostate	1 (4.3)	1 (14.3)	11 (23.4)	2 (22.2)	15 (17.4)
Kidney	7 (30.4)	1 (14.3)	2 (4.3)	0	10 (11.6)
Lung	3 (13.0)	1 (14.3)	4 (8.5)	2 (22.2)	10 (11.6)
Lymphoma[a]	0	0	8 (17.0)	0	8 (9.3)
Colon	1 (4.3)	2 (28.6)	4 (8.5)	0	7 (8.1)
Head/neck	2 (8.7)	0	3 (6.4)	0	5 (5.8)
Other[b]	1 (4.3)	0	3 (6.4)	1 (11.1)	5 (5.8)
Peritoneum	0	1 (14.3)	2 (4.3)	1 (11.1)	4 (4.7)
Thyroid[c]	1 (4.3)	1 (14.3)	2 (4.3)	0	4 (4.7)
Breast	0	0	3 (6.4)	0	3 (3.5)
Pancreas	1 (4.3)	0	0	2 (22.2)	3 (3.5)
Bladder	2 (8.7)	0	0	0	2 (2.3)
Stomach	1 (4.3)	0	0	1 (11.1)	2 (2.3)
Esophagus	0	0	1 (2.1)	0	1 (1.2)
Cervix	1 (4.3)	0	0	0	1 (1.2)

Liver	0	0	1 (2.1)	0	1 (1.2)
Oral	1 (4.3)	0	0	0	1 (1.2)
Ovary	0	0	1 (2.1)	0	1 (1.2)
Pleura	0	0	1(2.1)	0	1 (1.2)
Soft tissue sarcoma	1 (4.3)	0	0	0	1 (1.2)
Skin melanoma	0	0	1 (2.1)	0	1 (1.2)

[a]Includes cutaneous T-cell lymphoma (n=4), peripheral T-cell lymphoma (n=3), and non-Hodgkin lymphoma (n=1)
[b]Includes intraabdominal, mesentery, perinephric, trachea, and unknown primary with liver metastases
[c]Includes follicular thyroid
BSA, body surface area; WHO, World Health Organization

Table 2. Summary of MTD and dose-limiting toxicities

Study Arm Dose, mg/m^2	Pts Treated	Pts MTD-Evaluable[a]	Pts With DLTs	Type of DLT Event (n)	Grade
Arm 1					
1.2	2	2	0	N/A	N/A
2.4	3	3	0	N/A	N/A
4.8	3	3	0	N/A	N/A
7.2 (MTD)	7	6	1	Thrombocytopenia (1)	2
9.0	8	8	5	Thrombocytopenia (3); neutropenia (2); hyperbilirubinemia (1)	4,4,4; 3,4; 3
Arm 2[b]					
2.4	1	1	0	N/A	N/A
4.8	1	1	0	N/A	N/A
9.6	1	1	0	N/A	N/A
20.0	1	1	1	Torsades de pointes (1); sinus bradycardia (1); vomiting (1); dehydration (1); febrile neutropenia (1)	4; 3; 3; 3; 4
15.0	3	2	0	N/A	N/A
Arm 3					
10.0	8	6	0	N/A	N/A
15.0	8	7	0	N/A	N/A
20.0 (MTD)	8	7	1	Thrombocytopenia (1)	4
Arm 4[b,c]					
25.0	3	2	1	Fatigue (1)	3
20.0	6	6	1	Fatigue (1); prolonged QTc (1)	3; 3

[a] The number of evaluable patients includes all patients accrued in the dose-escalation phase meeting MTD-evaluable criteria and may differ from the total number of evaluable patients available for this phase
[b] Formal MTD was for this arm
[c] The starting dose for Arm 4 was 25.0 mg/m^2
DLT, dose-limiting toxicity; MTD, maximum tolerated dose; N/A, not applicable; Pts, patients

Table 3. All-grade adverse events listed by treatment arm, total >20%

Adverse Event n (%)	Panobinostat Dosing Arm		
	Arm 1 n=23	Arm 3 n=47	Total N=70
Fatigue	10 (43.5)	36 (76.6)	46 (65.7)
Thrombocytopenia	14 (60.9)	25 (53.2)	39 (55.7)
Nausea	6 (26.1)	31 (66.0)	37 (52.9)
Anemia	7 (30.4)	26 (55.3)	33 (47.1)
Decreased appetite	3 (13.0)	27 (57.4)	30 (42.9)
Constipation	5 (21.7)	17 (36.2)	22 (31.4)
Dyspnea	0	22 (46.8)	22 (31.4)
Vomiting	3 (13.0)	19 (40.4)	22 (31.4)
Diarrhea	4 (17.4)	17 (36.2)	21 (30.0)
Hypomagnesemia	0	21 (44.7)	21 (30.0)
Pyrexia	3 (13.0)	17 (36.2)	20 (28.6)
Hypotension	0	20 (42.6)	20 (28.6)
Dehydration	0	17 (36.2)	17 (24.3)
Dizziness	0	16 (34.0)	16 (22.9)
Hypokalemia	4 (17.4)	12 (25.5)	16 (22.9)
Peripheral edema	0	16 (34.0)	16 (22.9)

Table 4. Grade 3/4 adverse events listed by treatment arm

Adverse Event n (%)	Panobinostat Dosing Arm		
	Arm 1 n=23	Arm 3 n=47	Total N=70
Thrombocytopenia	8 (34.8)	19 (40.4)	27 (38.6)
Fatigue	1 (4.3)	9 (19.1)	10 (14.3)
Anemia	2 (8.7)	7 (14.9)	9 (12.9)
Dyspnea	0	6 (12.8)	6 (8.6)
Neutropenia	0	5 (10.6)	5 (7.1)
Pneumonia	0	5 (10.6)	5 (7.1)
Cognitive disorder	0	3 (6.4)	3 (4.3)
Dehydration	0	3 (6.4)	3 (4.3)
Gastrointestinal	1 (4.3)	2 (4.3)	3 (4.3)
Hypoxia	0	3 (6.4)	3 (4.3)
Leukopenia	3 (13.0)	0	3 (4.3)
Ascites	0	2 (4.3)	2 (2.9)
Back pain	0	2 (4.3)	2 (2.9)
Hyperglycemia	0	2 (4.3)	2 (2.9)
Anxiety	0	1 (2.1)	1 (1.4)
Dizziness	0	1 (2.1)	1 (1.4)
Dysuria	0	1 (2.1)	1 (1.4)
Hypokalemia	0	1 (2.1)	1 (1.4)
Hypomagnesemia	0	1 (2.1)	1 (1.4)
Hypotension	0	1 (2.1)	1 (1.4)
Pain in extremities	0	1 (2.1)	1 (1.4)
Pyrexia	0	1 (2.1)	1 (1.4)

Table 5. Mean panobinostat pharmacokinetic parameters for doses on day 1

	Pharmacokinetic Parameters				
Dose, mg/m^2	C_{max}, ng/mL±SD	$AUC_{0-\infty}$, ng•h/mL±SD	CL, L/h±SD	V_z, L±SD	$T_{1/2}$, h±SD
1.2	37.3±5.09	N/A	N/A	N/A	N/A
2.4[a]	62.3±5.97	N/A	N/A	N/A	N/A
4.8[a]	78.8±57.85	N/A	N/A	N/A	N/A
7.2	252.2±36.88	258.0±85.32	55.6±21.45	820.0±477.08	9.8±2.19
9.0	290.9±116.04	416.0±88.34	41.4±12.26	516.0±94.56	9.1±2.53
10.0	419.0±219.42	518.1±113.43	36.9±8.03	794.7±289.06	14.8±3.18
15.0[a]	619.4±155.76	912.9±353.74	35.7±13.73	741.4±385.52	14.6±5.27
20.0[a]	783.5±350.20	1040.6±397.78	45.2±19.75	1131.8±635.66	17.1±4.67

[a] Pharmacokinetic parameters include all patients treated at these doses regardless of assigned arm
$AUC_{0-\infty}$, area under the concentration–time curve from time zero to infinity; CL, total body clearance; C_{max}, maximum plasma drug concentration; N/A, not applicable; SD, standard deviation; $t_{1/2}$, terminal half-life; V_z, volume of distribution

Table 6. Positive histone acetylation response by treatment arm and dose (full analysis set)

Treatment Arm	Dose, mg/m^2	Evaluable response[a] n	Positive reading[b] n, (%)
Arm 1	4.8	3	3 (100.0)
	7.2	4	3 (75.0)
	9.0	6	6 (100.0)
	All	13	12 (92.3)
Arm 3	10.0	8	8 (100.0)
	15.0	8	8 (100.0)
	20.0	27	27 (100.0)
	All	43	43 (100.0)

[a] Evaluable patients were those with a reading at baseline and at least one post-baseline time point
[b] A positive reading was defined as a >2-fold increase in histone acetylation compared with baseline

Supplementary Table 1. Histone acetylation in PBMCs by time point, schedule, and dose (Arm 1)

Timepoint	1.2 mg/m^2 N=2	2.4 mg/m^2 N=3	4.8 mg/m^2 N=3	7.2 mg/m^2 N=7	9.0 mg/m^2 N=8	All N=23
Cycle 1, day 1 (1 hr); n/N (%)	–	–	3/3 (100.0)	3/4 (75.0)	5/5 (100.0)	11/12 (91.7)
Cycle 1, day 1 (3 hr); n/N (%)	–	–	3/3 (100.0)	2/4 (50.0)	5/5 (100.0)	10/12 (83.3)
Cycle 1, day 1 (6 hr); n/N (%)	–	–	2/3 (66.7)	3/4 (75.0)	5/5 (100.0)	10/12 (83.3)
Cycle 1, day 3 (0 hr); n/N (%)	–	–	3/3 (100.0)	3/3 (100.0)	5/5 (100.0)	11/11 (100.0)
Cycle 1, day 3 (1 hr); n/N (%)	–	–	3/3 (100.0)	3/3 (100.0)	4/5 (80.0)	10/11 (90.9)
Cycle 1, day 3 (3 hr); n/N (%)	–	–	1/2 (50.0)	2/2 (100.0)	5/5 (100.0)	8/9 (88.9)
Cycle 1, day 3 (6 hr); n/N (%)	–	–	3/3 (100.0)	3/3 (100.0)	5/5 (100.0)	11/11 (100.0)
Cycle 1, day 4 (0 hr); n/N (%)	–	–	3/3 (100.0)	3/3 (100.0)	5/5 (100.0)	11/11 (100.0)
Cycle 1, day 8 (0 hr); n/N (%)	–	–	2/2 (100.0)	2/2 (100.0)	5/6 (83.3)	9/10 (90.0)
Cycle 1, day 15 (0 hr); n/N (%)	–	–	–	–	0/1 (0.0)	0/1 (0.0)
Any time	–	–	3/3 (100.0)	3/4 (75.0)	6/6 (100.0)	12/13 (92.3)

Supplementary Table 2. Histone acetylation in PBMCs by time point, schedule, and dose (Arm 3)

Timepoint	10 mg/m^2 N=8	15 mg/m^2 N=8	20 mg/m^2 N=31	All N=47
Cycle 1, day 1 (1 hr); n/N (%)	8/8 (100.0)	6/7 (85.7)	25/27 (92.6)	39/42 (92.9)
Cycle 1, day 1 (3 hr); n/N (%)	7/7 (100.0)	6/7 (85.7)	22/24 (91.7)	35/38 (92.1)
Cycle 1, day 1 (6 hr); n/N (%)	7/7 (100.0)	6/7 (85.7)	26/27 (96.3)	39/41 (95.1)
Cycle 1, day 8 (0 hr); n/N (%)	0/5 (0.0)	3/7 (42.9)	12/21 (57.1)	15/33 (45.5)
Cycle 1, day 8 (1 hr); n/N (%)	5/5 (100.0)	7/7 (100.0)	19/22 (86.4)	31/34 (91.2)
Cycle 1, day 8 (3 hr); n/N (%)	5/5 (100.0)	7/7 (100.0)	20/20 (100.0)	32/32 (100.0)
Cycle 1, day 8 (6 hr); n/N (%)	5/5 (100.0)	6/7 (85.7)	21/22 (95.5)	32/34 (94.1)
Cycle 1, day 9 (0 hr); n/N (%)	4/6 (66.7)	7/7 (100.0)	18/21 (85.7)	29/34 (85.3)
Cycle 1, day 15 (0 hr); n/N (%)	2/5 (40.0)	2/5 (40.0)	7/16 (43.8)	11/26 (42.3)
Any time	8/8 (100.0)	8/8 (100.0)	6/6 (100.0)	43/43 (100.0)

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