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CLINICAL TRIAL REPORT

A phase I, open-label, multicenter study to evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function

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Abstract
Purpose To evaluate the pharmacokinetics and safety of oral panobinostat in patients with advanced solid tumors and varying degrees of hepatic function.
Methods Patients with advanced solid malignancies, acceptable bone marrow and renal function, and normal or impaired hepatic function, per NCI-ODWG criteria, were eligible. Initially patients received a single oral dose of 30 mg panobinostat for a 1-week pharmacokinetic study (core phase). Subsequently, patients received thrice-weekly panobinostat for as long as beneficial (extension phase safety assessment). Core phase serial blood samples for panobinostat and metabolite BJB432 assay were collected pre-dose and up to 96 h post-dose.
Results Twenty-five patients were enrolled, median age 58 years (range 45–76). Fifteen patients had hepatic dysfunction (8 mild, 6 moderate, and 1 severe). Reductions in panobinostat plasma clearance were 30 and 51 %, with concomitant 43 and 105 % increase in exposure, for patients with mild and moderate hepatic dysfunction, respectively. Median peak plasma concentrations were 1.4-(mild) and 1.8-(moderate) fold higher than the normal group. Hepatic impairment did not alter panobinostat absorption with Tmax unchanged at 2 h. Geometric mean ratios of BJB432 to panobinostat plasma $AUC_{0-\infty}$ were similar in patients with normal, mild, or moderate hepatic impairment. Safety data were consistent with known safety profile of panobinostat in patients with advanced cancers and normal liver function.
Conclusion Despite increased plasma exposure, patients with mild or moderate hepatic dysfunction could be safely treated with the same starting dose of panobinostat as patients with normal hepatic function, with careful monitoring and dose adjustments as required.

Keywords Panobinostat · Hepatic impairment · Pan-deacetylase inhibitor · Histone · Phase I

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Introduction

Panobinostat is a potent pan-deacetylase inhibitor (pan-DACi) with low nanomolar activity against all classes I,

Table 1 Definition of hepatic function groups and scheme of planned dose levels in study part 2 (extension phase)

NCI-ODWG hepatic function/impairment group				
	Normal	Mild	Moderate	Severe
Bilirubin level	≤ULN	≤ULN >1.0–1.5ULN	>1.5–3ULN	>3ULN
AST level	≤ULN	AST > ULN Any AST	Any AST	Any AST
Dose level	Panobinostat dosing schedule			
Starting dose	30-mg TIW QW	30-mg TIW QW	30-mg TIW QW	30-mg TIW QOW
Dose level 1	30-mg TIW QOW	30-mg TIW QOW	30-mg TIW QOW	20-mg TIW QOW
Dose level 2	20-mg TIW QOW	20-mg TIW QOW	20-mg TIW QOW	

AST aspartate aminotransferase, *ULN* upper limit of normal, *TIW* three times a week, *QW* weekly, *QOW* Every other week

II, and IV histone deacetylase enzymes [1, 2]. This activity is exerted by direct inhibition of histone deacetylases, modulating both histone and nonhistone proteins that regulate various cell signaling pathways [3–7]. Panobinostat has shown preclinical and clinical activity as monotherapy and in combination with other chemotherapeutic agents in multiple tumor types [8–13]. The common toxicities associated with panobinostat include fatigue, thrombocytopenia, nausea, vomiting, and diarrhea. The disposition, metabolism, and excretion of panobinostat were studied in advanced cancer patients via trace radiolabeled [^{14}C] material. These studies indicate that both liver and kidney are involved in the metabolism and elimination of the parent compound [14]. The elimination is primarily in the form of metabolites with unchanged panobinostat in urine and feces accounting for <2.5 and <3.5 % of the dose, respectively [14]. Panobinostat and its numerous inactive metabolites are excreted almost equally in bile/feces (44–77 % of the dose) and urine (29–51 % of the dose). Metabolite BJB432 is formed from the initial reduction of panobinostat hydroxamic acid side chain and does not inhibit DAC. It has moderate in vitro affinity (IC_{50} of 1.6 μM) toward human ether-a-go-go-related-gene (hERG) potassium ion (K^+) channels, but has shown no contributing effect on QT prolongation [15]. BJB432 has previously been referred to by other names in the medical literature including M37.8 [14] and M4 [16].

To date, the safety and pharmacokinetics (PK) of panobinostat have been characterized in cancer patients with adequate hepatic function and no data are available in patients with hepatic dysfunction. Patients with advanced malignancies and impaired organ function often require dose adjustments of a given anticancer agent depending on its route of biotransformation or elimination. Thus, PK and safety studies in patients with hepatic dysfunction are important to guide dosage in this setting, and thereby avoid preventable toxicities.

Therefore, we conducted a phase I open-label multicenter study to evaluate the PK and safety of oral panobinostat and its metabolite BJB432 in patients with advanced solid tumors and varying degrees of hepatic impairment.

Patients and methods

Study design

Eligible patients were stratified by the degree of hepatic dysfunction. The National Cancer Institute Organ Dysfunction Working Group (NCI-ODWG) criteria [17] for classifying hepatic dysfunction as normal, mild, moderate, and severe based on serum bilirubin and AST (aspartate transaminase) levels are given in Table 1. The sample size was based on FDA guidance for the industry with planned 22–28 evaluable patients dosed in the PK study [18].

The study comprised of 2 parts. Part 1 (core phase) evaluated the PK of panobinostat in each hepatic function group after a single, 30-mg oral dose with food. Blood sampling was carried out pre-dose and over 96 h post-dose. Part 2 (extension phase) was initiated 7 days after the start of core phase to characterize the safety profile of panobinostat. Panobinostat 30 mg/day was administered three times a week, weekly or every other week, depending on the patient's degree of hepatic dysfunction. In patients with severe liver dysfunction, a lower starting dose of 20-mg panobinostat three times a week every other week was also considered based on safety data from the mild and moderate group. Treatment cycles were repeated every 28 days (Table 1).

Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of informed consent. Initially, patients with normal hepatic function and mild or moderate hepatic dysfunction were enrolled in the study. A decision to enroll patients with severe hepatic impairment was made following review of the preliminary safety data of all patients who completed the core phase and cycle 1 of the extension phase, which included at least three patients from the moderate hepatic dysfunction group.

Eligibility criteria

Patients with normal or abnormal liver function (including those with liver metastases and the presence of biliary

stents), an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, and age ≥18 years were considered eligible if they had a documented diagnosis of advanced solid tumor for which no standard systemic therapy exists. Exclusion criteria were prior DACi's, valproic acid treatment, any concomitant anticancer therapy, use of medication that affects renal or hepatic function, active central nervous system disease or brain metastasis, evidence of another malignancy not in remission, or any other concurrent severe or uncontrolled medical condition.

Pharmacokinetic assessments

Serial whole-blood samples for PK analysis were collected in the core phase on day 1 at pre-dose and 0.5 (30 min), 1, 2, 4, 7, 24 (day 2), 48 (day 3), 72 (day 4), and 96 (day 5) hours post-dose. Approximately 40 mL blood was collected per patient, and this included a 3-mL sample collected pre-dose for protein binding analysis. Plasma was assayed for panobinostat and BJB432 concentration using a validated liquid chromatography tandem mass spectrometry (LC–MS/MS) method [14, 19]. Percent protein binding at baseline was assessed ex vivo by radiolabeling each plasma sample using [^{14}C]-panobinostat. Percent protein binding of panobinostat was quantified by spiking pre-dose patient plasma samples with panobinostat to achieve 30 and 100 ng/mL concentration levels. These concentrations represent the typical and highest Cmax achievable in humans after oral administration of panobinostat at the tested dose range of 10–80 mg.

Statistical assessments

Pharmacokinetics parameters were estimated using non-compartmental analysis. PK parameters including peak plasma concentration Cmax, time to reach peak plasma concentration Tmax, area under curve $AUC_{0-\infty}$ and AUClast, last observable concentration Clast, time to last concentration Tlast, elimination half-life T1/2, total body clearance CL/F, and apparent volume of distribution Vz/F were derived based on analysis of plasma panobinostat concentration data and replicated for the metabolite BJB432. A linear mixed model analysis was performed to account for differences in age and body surface area (BSA). For this analysis, groups with various degrees of liver dysfunction were tested against the reference normal group with corrections being applied for baseline BSA and age. The point estimate of the treatment difference and the corresponding 90 % confidence intervals (CI) were calculated and antilogged to obtain the point estimate and CI on the linear scale for the ratio of geometric means of the test as compared with the reference. For Tmax, point estimates with 90 % CI were calculated using nonparametric methods [20, 21]. Summary statistics were presented for panobinostat and its metabolite with geometric mean and CV % (minimum and maximum).

Patient assessments

Patients underwent a complete physical examination and assessment of ECOG at baseline. Physical examination and ECOG were repeated before day 1 of each treatment cycle in the extension phase. Total bilirubin and AST were evaluated at baseline before start of core phase. Blood profile and thyroid function analyses were carried out at baseline and before day 1 of each cycle in the extension phase. Central 12-lead ECGs were collected at baseline and at specified time-points (pre-and post-dose) in the core and extension phase. Adverse events (AE) were graded according to NCI-CTCAE, version 3.0 [22] and recorded throughout the study until 28 days after the last dose of panobinostat.

Treatment modifications

In the extension phase, patients were required to have resolution of treatment-emergent hematologic toxicities to grade ≤2 or baseline and of all other toxicities to grade ≤1 before initiation of each treatment cycle. During the course of the cycle, panobinostat treatment was paused in the event of grade 3 gastro-intestinal (GI) toxicity and grade 3–4 hematologic or non-hematologic toxicities. Uncontrolled grade 4 GI toxicity required permanent treatment discontinuation. Hepatic toxicity was handled according to the hepatic function of the patient. Grade 3 bilirubin in patients with normal liver function, or with mild-to-moderate hepatic impairment, required temporary discontinuation of dosing until recovery to grade 1 or grade 2 bilirubin levels. In patients with severe hepatic impairment and treatment-emergent bilirubin >1.5× baseline, treatment was held until recovery to ≤baseline values. Treatment-emergent cardiac AEs required permanent treatment discontinuation in case of absolute QTcF values ≥480 ms or relative to baseline changes >60 ms. In all cases, treatment was restarted at the same dose if toxicities resolved within 7 days. A lower dose level was considered if recovery required more than 7 days. Toxicity-related inability to start a new cycle within 2 weeks of the scheduled date resulted in removal of the patient from study.

Tumor assessments were performed at baseline and followed up during the course of the study according to RECIST criteria, version 1.0 [23]. With efficacy being an exploratory study endpoint, the best overall response at the end of treatment was based on the investigator's evaluation. No formal analysis of tumor measurements was conducted for this study.

Table 2 Patient disposition and baseline characteristics overall and by hepatic function group

Panobinostat dose core PK phase, *n* (%)	Hepatic function/impairment group				
	All ($n = 25$)	Normal ($n = 10$)	Mild ($n = 8$)	Moderate ($n = 6$)	Severe ($n = 1$)
30-mg single dose	25 (100)	10 (100)	8 (100)	6 (100)	1 (100)
Extension phase, n (%)					
30-mg TIW QW	24 (96)	10 (100)	8 (100)	6 (100)	
Evaluable for PK, *n* (%)	24 (96)	10 (100)	7 (87.5)	6 (100)	1 (100)
Evaluable for safety, *n* (%)	25 (100)	10 (100)	8 (100)	6 (100)	1 (100)
Median age, year (range)	58 (45–76)	52 (45–76)	54 (46–67)	65 (59–74)	58 (58–58)
Male, *n* (%)	14 (56)	4 (40)	4 (50)	5 (83)	1 (100)
Female, *n* (%)	11 (44)	6 (60)	4 (50)	1 (16.7)	
Caucasian, *n* (%)	25 (100)	10 (100)	8 (100)	6 (100)	1 (100)
Cancer type, n (%)					
Colon	6 (24)	1 (10)	1 (12.5)	3 (50)	1 (100)
Prostate	3 (12)	1 (10)	1 (12.5)	1 (16.7)	0
Rectum	3 (12)	0	2 (25)	1 (16.7)	0
Lung	2 (8)	1 (10)	1 (12.5)	0	0
Uterus	2 (8)	2 (20)	0	0	0
Others[a]	9 (45)	5 (50)	3 (37.5)	1 (16.7)	0
ECOG PS, n (%)					
0	7 (28)	5 (50)	0	2 (33.3)	0
1	17 (68)	5 (50)	7 (87.5)	4 (66.7)	1 (100)
2	1 (4)	0	1 (12.5)	0	0

[a] Including 1 mesothelioma, 1 gastric, 1 peritoneum, 1 melanoma, 1 fallopian tubes (normal group); 1 gall bladder, 1 ovarian, 1 endometrium (mild group); 1 liver (moderate group)

Results

Patient disposition and baseline characteristics

A total of 25 patients were enrolled in the study and received oral panobinostat (10 patients with normal hepatic function, 8 and 6 patients with mild and moderate hepatic impairment, respectively). One patient with severe hepatic impairment was subsequently enrolled and received the single PK dose of 30 mg panobinostat and completed the PK assessments during the core phase before withdrawing due to increased bilirubin levels; this patient was included in the PK and safety population. One patient in the mild hepatic impairment group was excluded from the PK population due to vomiting within 4 h of the single PK dose of panobinostat. Patient disposition and baseline characteristics, overall and by hepatic function group, are summarized in Table 2. Overall, the median age was 58 years (range 45–76); 56 % of patients were male; and 28, 68, and 4 % of patients had an ECOG performance status of 0, 1, and 2, respectively. The most common malignancy was colon cancer, seen in 24 % of patients.

Patient exposure

All patients took 30 mg panobinostat during the PK core phase. Thereafter, all patients started the extension phase with the dose regimen of 30-mg three times a week, weekly. None received the lowest dose level of 20-mg/day three times a week, every other week. Patients received a median of 1 cycle of treatment (range 0.1–3.7) including medians (ranges) of 1.2 (0.1–3.5), 0.9 (0.1–2.2), and 1.6 (0.5–3.7) in patients with normal hepatic function, mild, and moderate hepatic impairment, respectively. Three patients received $\geq$2 cycles. The mean duration of exposure in the extension phase was 1.35 months in all patients. Overall 76 % of patients received $\leq$2 months of treatment. Most patients required dose reduction to 30-mg three times a week, every other week (instead of weekly) within the first 2 weeks of treatment. Patients received a median of 7.8 mg/day of panobinostat (range 0.0–12.9), representing 60 % of the median planned dose of 12.9 mg/day. The mean relative dose intensity (DI) was 0.63 in all patients with slightly higher values in patients with mild liver impairment (0.73).

The main reason for treatment discontinuation was disease progression in 18 (72 %) patients, including 9 (90 %),

Table 3 Summary of panobinostat and BJB432 plasma PK profile by hepatic function group

	Hepatic function/impairment group			
	Normal ($n = 10$)	Mild ($n = 7$)	Moderate ($n = 6$)	Severe ($n = 1$)
Panobinostat PK parameter (*unit*)				
T_{max} (h)	2.0 (0.5–7.0)	2.0 (0.5–4.0)	2.0 (1.0–4.0)	2.0 (2.0–2.0)
C_{max} (ng/mL)	18.5 (81.2)	29.1 (57.3)	33.9 (50.9)	31.2 (NE)
$AUC_{0–48}$ (ng h/mL)	125.0 (70.3)	183.9 (54.2)	249.9 (43.2)	235.4 (NE)
$AUC_{0–\infty}$ (ng h/mL)	150.3 (72.3)	214.8 (56.3)	308.0 (44.2)	272.3 (NE)
AUC_{last} (ng h/mL)	140.5 (73.3)	204.3 (56.2)	284.9 (42.6)	263.9 (NE)
CL/F (mL/h)	199,647 (72.3)	139,658 (56.3)	97,399 (44.2)	110,187 (NE)
Vz/F (mL)	8,295,077 (54.7)	5,826,678 (48.1)	4,863,991 (35.1)	3,156,940 (NE)
$T_{1/2}$ (h)	28.8 (27.3)	26.3 (27.6)	34.6 (31.5)	19.9 (NE)
C_{last} (ng/mL)	0.24 (0.13–0.42)	0.27 (0.11–0.46)	0.52 (0.17–0.61)	0.29 (NE)
T_{last} (h)	96.0 (47.9–96.3)	96.0 (72.0–96.6)	96.0 (95.8–96.0)	96.0 (96.0–96.0)
BJB432 PK parameter (*unit*)				
T_{max} (h)	24.0 (2.0–48.0)	2.0 (2.0–24.2)	24.0 (4.0–48.0)	48.0 (48.0–48.0)
C_{max} (ng/mL)	2.5 (108.3)	2.2 (77.6)	2.8 (42.9)	2.6 (NE)
$AUC_{0–\infty}$ (ng h/mL)	183.9 (108.7)	132.9 (110.2)	308.3 (29.3)	190.2 (NE)
CL/F (mL/h)	163,110 (108.7)	225,788 (110.2)	97,313 (29.3)	157,762 (NE)
$T_{1/2}$ (h)	40.5	37.5	61.2	30.7
Ratio of $AUC_{0–\infty}$ BJB432/panobinostat	1.2	0.62	1.0	0.7

Values are geometric mean (%CV), except for C_{last}, T_{max}, and T_{last} (median; range)

T_{max} the time to reach maximum (peak) plasma drug concentration after single dose administration (h), C_{max} the maximum (peak) observed plasma drug concentration after single dose administration (ng/mL), $AUC_{0–48h}$ the AUC from time zero to 48 h (ng h/mL), $AUC_{0–\infty}$ the AUC from time zero to infinity (ng h/mL), AUC_{last} the area under the concentration–time curve from time zero to the time of the last measurable sample (amount × time × vol^{-1}), *Cl/F* the total body clearance of drug from the plasma (L/h), *Vz/F* the apparent volume of distribution during terminal phase (associated with λz), $T_{1/2}$ the elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration–time curve (h), C_{last} (*ng/mL*) the last measurable concentration at time T_{last}, T_{last} the time at the last measurable concentration (h), *NE* not evaluable

5 (62.5 %), and 4 (67 %) patients in the normal function, mild, and moderate hepatic impairment groups, respectively. In addition, 3 (12 %) patients refused further participation and 4 (16 %) discontinued because of AEs.

Pharmacokinetics

Pharmacokinetic samples and data were available for 24 patients across the hepatic function groups. PK parameters from non-compartmental analysis grouped by hepatic function are listed in Table 3. Mean plasma concentration profiles for panobinostat are presented in Fig. 1a and mean plasma concentration–time profiles for BJB432 are presented in Fig. 1b. The absorption of panobinostat was not affected by hepatic function as median Tmax was similar across all groups. The median $AUC_{0–\infty}$ in the mild and moderate hepatic function group was approximately 35 and 84 % higher than the normal group. Individual estimates of the $AUC_{0–\infty}$ between mild and normal group largely overlapped. Geometric mean of $AUC_{0–\infty}$ in the normal, mild, and moderate group were 150.3, 214.8, and 308.0 ng h/mL, respectively (shown in Fig. 2). This represents a 43 % increase in the mild and 105 % increase in the moderate groups as compared with the normal group. The percent coefficient of variance (CV) associated with the geometric mean was large, ranging between 44 and 72 %, and reflected the large PK variability of panobinostat. After adjusting for baseline age and BSA in a linear mixed model analysis, the adjusted geometric means $AUC_{0–\infty}$ were similar to the unadjusted geometric means in the normal and mild group and slightly lower in the moderate group at 151.6, 214.6, and 291.8 ng h/mL, respectively. This represents a 42 % increase in the mild and a 92 % increase in the moderate groups when compared with the normal group. The geometric mean $AUC_{0–\infty}$ values for BJB432 were 183.9, 132.9, and 308.3 ng h/mL in the normal, mild, and moderate liver dysfunction groups, respectively. Geometric mean ratio of $AUC_{0–\infty}$ of BJB432 over the parent compound (panobinostat) was 1.2 in patients with normal liver function and 0.62, 1.0, and 0.7 in patients with mild, moderate, and severe liver dysfunction, respectively. Median peak plasma concentration of panobinostat Cmax was 1.4-fold (mild) and 1.8-fold (moderate) higher than the normal group, but the Cmax of BJB432 was similar across all hepatic dysfunction

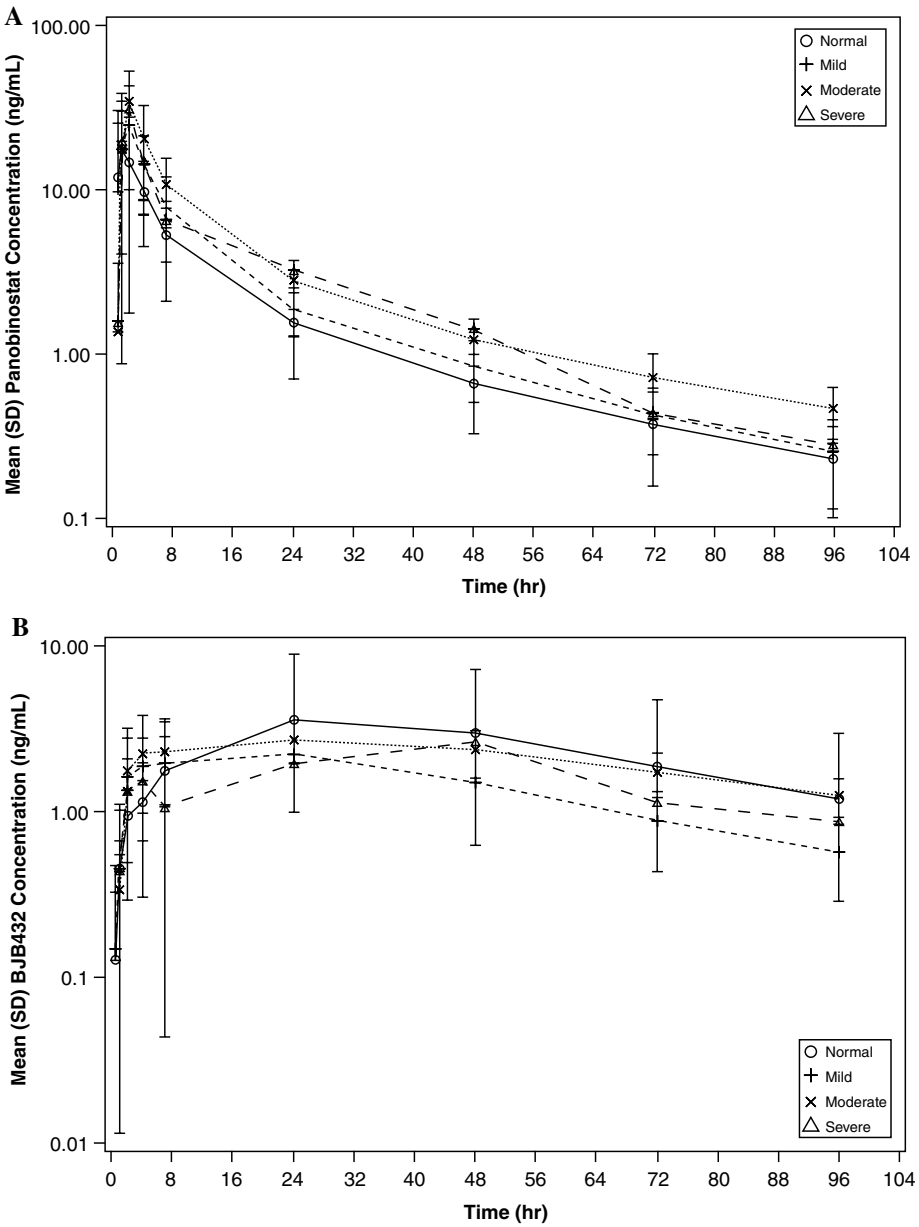

Fig. 1 **a** Arithmetic mean (SD) of panobinostat plasma concentration–time profiles following a single 30-mg dose, stratified by hepatic function (core phase). **b** Arithmetic mean (SD) of BJB432 plasma concentration–time profiles following a single 30-mg dose, by hepatic function groups (core phase)

groups. The terminal half-life of panobinostat estimated across normal, mild, and moderate groups were similar, between 26 and 35 h. The terminal half-life of BJB432 was longer, between 37 and 61 h for the normal, mild, and moderate groups. This is consistent with the terminal half-life derived from the final parameter estimates of the population PK analysis in patients with normal hepatic function. Using Child–Pugh's classification [24], patients with mild and moderate liver impairment had median panobinostat exposures of approximately 51 and 56 % above the normal group (the severe patient was categorized as moderate according to Child–Pugh criteria). Percent panobinostat bound to plasma protein was similar at panobinostat concentrations of 30 and 100 ng/mL. At clinically relevant peak plasma concentration of 30 ng/mL, percent protein binding in the mild impairment group was similar to those in the normal group at 83 % and decreased to 77 and 74 % in the moderate and severe group, respectively. Panobinostat protein binding adjusted free $AUC_{0-\infty}$ values for the normal, mild, and moderate groups were 24.7, 36.3, and 70.4 ng h/mL, respectively. PK parameters of the severe patient did not differ from those of the moderate group.

No patient received concomitant CYP3A4 inhibitors or inducers during the study core PK phase, thus the data in this study were not affected by such medications.

Safety

All patients treated with panobinostat experienced at least one AE, and AEs of grade ≥3 were recorded for

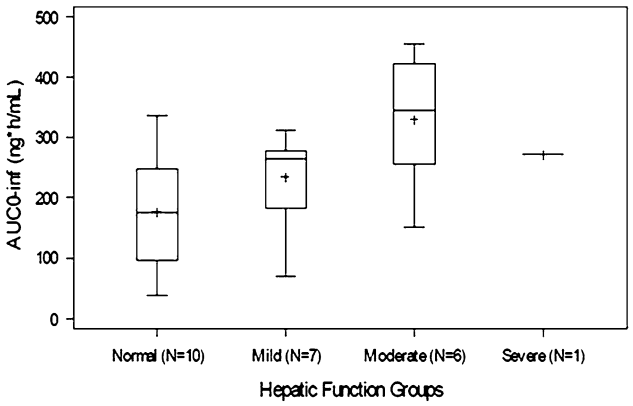

Fig. 2 *Box plot* of panobinostat-unadjusted $AUC_{0-\infty}$ following a single 30-mg dose by hepatic function (core phase). $AUC_{0-\infty}$ not adjusted for baseline age and BSA; plus represents the mean; the *lower and upper whiskers* extend to the most extreme points within 1.5*IQR (interquartile range)

92 % of patients. The safety profile of panobinostat and the most common drug-related AEs (all grades, and grade ≥3) are summarized in Table 4 stratified by hepatic function group. Rates of grade ≥3 drug-related AEs were 70 % in patients with normal liver function, 62.5 and 83.3 % in patients with mild and moderate liver impairment, respectively. Fatigue, nausea, thrombocytopenia, and diarrhea were the most common drug-related AEs of grade ≥3. These included grade 4 fatigue in one patient with mild hepatic impairment and grade 4 thrombocytopenia in 2 patients with normal hepatic function and 3 patients with moderate hepatic impairment. The observed severity of thrombocytopenia was not related to the degree of hepatic impairment or baseline platelet count in this study. Serious adverse events (SAEs) were reported in 36 % of patients, mostly patients with normal liver function. The most common drug-related SAEs were diarrhea, nausea, vomiting, and fatigue (2 patients each). Overall, 4 patients (16 %) had at least one AE leading to study drug discontinuation, fatigue being the most frequent. One unexpected SAE (grade 3 vasculitis) occurred during this study in a patient with moderate hepatic impairment. There were no clinically significant changes in hematology or biochemistry parameters. The most frequently reported biochemical abnormality was an increase in total bilirubin (grade 3, in five patients, four with moderate liver impairment and 1 with mild liver impairment). Elevated levels of AST (grade 3) were seen in 2 patients, 1 with mild and 1 with moderate liver impairment. Grade 4 bilirubin level was noted at the end of the PK core phase in the patient with severe hepatic impairment who had enrolled with grade 3 bilirubin level. For this patient the elevation in liver function tests was not considered drug related. The safety data from this study was consistent with the known safety profile of single-agent oral panobinostat in patients with advanced cancers and adequate liver function.

A total of six patients died with five deaths occurring while on study treatment or within 28 days of the last dose of panobinostat, but these deaths were not treatment related. Most of the deaths were due to progression of underlying malignancy, and one death was recorded as pulmonary edema in the presence of disease progression.

Table 4 Safety profile of panobinostat overall and by hepatic function group, including most common drug-related adverse events of any grade (reported in ≥30 % of patients) and of grade ≥3 severity (reported in ≥10 % of patients)

Adverse event, *n* (%)	Hepatic function/impairment group				
	All $n = 25$	Normal $n = 10$	Mild $n = 8$	Moderate $n = 6$	Severe $n = 1$
Any adverse event (drug related)	22 (88)	9 (90)	7 (87.5)	6 (100)	0
Nausea	17 (68)	7 (70)	6 (75)	4 (66.7)	0
Fatigue	15 (60)	7 (70)	4 (50)	4 (66.7)	0
Vomiting	14 (56)	7 (70)	4 (50)	3 (50)	0
Decreased appetite	13 (52)	5 (50)	4 (50)	4 (66.7)	0
Thrombocytopenia	7 (28)	4 (40)	0 (0)	3 (50)	0
Diarrhea	10 (40)	6 (60)	4 (50)	0	0
Any grade ≥3 adverse event (drug related)	17 (68)	7 (70)	5 (62.5)	5 (83.3)	0
Fatigue	7 (28)	4 (40)	2 (25)	1 (16.7)	0
Nausea	4 (16)	3 (30)	1 (12.5)	0	0
Thrombocytopenia	4 (16)	3 (30)	0	1 (16.7)	0
Diarrhea	3 (12)	2 (20)	1 (12.5)	0	0
Any serious adverse event (drug related)	9 (36)	6 (60)	2 (25)	1 (16.7)	0
Discontinuation due to adverse event	4 (16)	1 (10)	1 (12.5)	1 (16.7)	1 (100)
On-study deaths	5 (20)	2 (20)	1 (12.5)	2 (33.3)	0

Efficacy

No complete or partial responses were observed for the 24 patients in the extension phase. Stable disease was the best overall response in 4 patients (16 %), including one in the normal group with lung cancer, one in the mild group with endometrial cancer, and two in the moderate group with prostate and liver cancer. Early progressive disease (PD) was noted in 14 patients (56 %).

Discussion

The primary objective of this study was to assess the effect of various degrees of impairment of hepatic function on the PK and safety of panobinostat. The FDA guidance [18] for industry recommends a PK study in patients with impaired hepatic function if hepatic metabolism and/or excretion accounts for a substantial portion (>20 % of the absorbed drug) of the elimination of a parent drug or active metabolite. This is essential for dosage recommendations in clinical practice.

This study used a design whereby all enrolled patients ($N = 25$) received a single initial fixed panobinostat dose. This optimizes PK comparisons across all hepatic function groups. Hepatic dysfunction classification, per NCI-ODWG criteria based on bilirubin level, is similar to other studies of anticancer agents [25–28]. This study showed that systemic exposure of panobinostat increased by 43 % in patients with mild hepatic impairment and 105 % in patients with moderate hepatic impairment. As imbalances in patient demographics may have contributed to the observed differences in the panobinostat plasma exposure between groups, adjustments were made for age and BSA in a linear mixed model analysis. The adjusted geometric means of the hepatic impairment groups were not substantially affected by age or BSA. Due to the large PK variability of panobinostat, adjusted geometric means of normal, mild, and moderate groups were associated with wide CI. The impact of change in adjusted geometric means seen between hepatic function groups was deemed not clinically significant, based on the covariates of BSA, age and race, on clearance, and central volume of distribution identified in the population PK analysis.

Metabolite BJB432/parent panobinostat plasma $AUC_{0-\infty}$ geometric mean ratios were similar in patients with normal, mild, and moderate hepatic impairment. This suggests that formation of BJB432 which is not mediated by CYP pathways was not affected by varying hepatic dysfunction. In patients with cancer, a study using the erythromycin breath test showed that moderate and severe hepatic impairment was associated with approximately 50 % reduction in CYP3A activity [29]. Panobinostat is extensively metabolized through both CYP and non-CYP-mediated pathways with CYP-mediated clearance ranging from 30 to 47 % of the dose [14]. For a drug like panobinostat that is not primarily and uniquely metabolized via CYP3A pathway, reduced CYP3A activity might not have a critical impact on panobinostat exposure.

In support of this assumption, another study in cancer patients indicated that co-administration of panobinostat with a strong CYP3A4 inhibitor ketoconazole increased panobinostat exposure by <twofold [30] with an estimated fraction of panobinostat cleared by CYP3A (fmCYP3A) of 0.4 [31]. These data reflect the relative contribution of CYP pathways (<50 %) to the overall metabolism of panobinostat.

Protein binding in the mild and normal group of 83 % was within the range of historical values, but slightly lower in the moderate and severe groups (77 and 74 %). The extent of increase in free $AUC_{0-\infty}$ in mild and moderate groups was somewhat similar to those not adjusted for protein binding, reflecting the limited role of protein binding on the free drug exposure for a moderately bound drug such as panobinostat.

Clinical safety profile of panobinostat was qualitatively and quantitatively consistent with known safety data in patients with advanced malignancies and adequate hepatic function treated in previous single-agent oral studies [3–5, 8–11]. The dose of 30 mg given three times a week on a weekly schedule was moderately tolerated by all patients regardless of their liver function. This is expressed by the low relative DI (0.63) seen in the majority of patients regardless of their liver function. The clinical relevance of liver function-related PK changes in regard to safety could not be fully established as increased exposures of panobinostat did not lead to corresponding increase in the main toxicities, thrombocytopenia or QTc prolongation. Grade 3/ Grade 4 GI dysfunction and fatigue did not differ significantly between the hepatic function groups at the given dose of 30 mg. With regard to thrombocytopenia, PK/PD modeling analyses have shown a dose-schedule-dependent relationship between oral panobinostat treatment and platelet response [32]. Since platelet kinetics is largely dependent on the baseline platelet count, tumor type, panobinostat dose and schedule, and systemic exposure alone are not sufficient to predict overall risk of thrombocytopenia. Schedule adjustment and/or dose reduction are effective at managing thrombocytopenia risk when patients experience decreased platelet counts during panobinostat treatment.

QTc prolongation has been identified as a possible concern during a phase I study with continuous intravenous administration of panobinostat [33]; however, in the current study as well as in the other studies using single-agent oral panobinostat, this does not seem to be a major issue [3–5, 9–11, 34]. The lack of QTcF signal evidenced by intensive

ECG monitoring throughout the study is consistent with historical data indicating a <1 % incidence of grade 3 QTc prolongation across the clinical oral dose range of 20–40 mg. In patients with normal or impaired liver function, the only observed QTc abnormalities were a few instances of increases in QTcF each less than <60 ms in one patient. In the current study, BJB432 did not affect cardiac function in any group of patients with hepatic dysfunction.

In summary, this PK study in cancer patients with varying degrees of hepatic impairment has shown that the systemic exposure of panobinostat increases with the severity of organ impairment. The extent of increase is less than twofold in the presence of moderate liver impairment. The systemic exposure of BJB432 is not significantly different between the three hepatic dysfunction groups (normal, mild, and moderate). The safety findings suggest that the increasing degree of hepatic impairment did not appear to substantially increase toxicity in the hepatic dysfunction groups and that the rates of grade ≥3 adverse events and SAEs in patients with hepatic impairment are within the same range as the rates in patients with normal hepatic function. Therefore, an exposure–response relationship for safety could not be established in patients with mild-to-moderate liver dysfunction. A limitation of the current study is the short duration of drug exposure (median 1.35 months) due to early disease progression in many patients. Additionally, small number of patients in the group with severe hepatic impairment suggests that caution is needed in administering panobinostat to this vulnerable patient population. This study demonstrated that exposure of panobinostat increases in patients with mild or moderate hepatic dysfunction, but without notable differences in safety. Therefore, patients with mild or moderate hepatic dysfunction could be safely treated with the same starting dose of panobinostat as patients with normal hepatic function, but should be closely monitored for adverse events and dose adjustments may be considered during therapy. This study has been complemented by a parallel trial of panobinostat in cancer patients with varying degrees of renal impairment, which has been recently completed.

Ethical standard The study was performed in accordance with ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The protocol was approved by the institutional review board of each participating institution with all patients providing written informed consent. The study was registered at clinicaltrials.gov with the identifier NCT01007968.

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