Sponsor

Novartis

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Advanced solid tumors

Approved Indication

Investigational

Protocol Number

CLBH589X2101

Title

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

Study Phase

I

Study Start/End Dates

30-Mar-2010 (first patient first visit)

30-Nov-2012 (last patient last visit)

Study Design/Methodology

This is a Phase I, open-label, multicenter study to evaluate the PK and safety of 30 mg oral panobinostat in patients with advanced solid tumors and various degrees of hepatic function (Group 1: normal; Group 2: mild; Group 3: moderate; Group 4: severe) as defined by NCI-CTEP criteria. It consists of a core Phase of 7 days and an extension Phase. In the core Phase, patients received a single oral dose of 30 mg panobinostat. Serial blood samples for assessing the PK of panobinostat were obtained at pre-specified time points. In the extension Phase, patients received 30 mg oral panobinostat three times weekly in 28-day cycles, until disease progression, unacceptable toxicity or withdrawal of consent. Dose reduction was allowed for the management of adverse events. Approximately 32 patients needed to be enrolled in order to have an adequate number of patients in the study (8 in Group 1; 6 in Group 2, 6 to 8 in Group 3, up to 6 in Group 4).

Centers

6 centers in 5 participating countries Sweden (2); United Kingdom (1); Switzerland (1); The Netherlands (1); United States (1).

Publication

None

Test Product (s), Dose(s), and Mode(s) of Administration

Oral panobinostat was supplied as 5 mg, 15 mg or 20 mg hard gelatin capsules and was given on a flat scale of mg on a given day. The capsules were packaged in HDPE bottles with plastic child resistant closures.

Statistical Methods

A formal statistical analysis was performed for PK parameters of panabinostat: T1/2, AUC0-48, AUC0-96, AUC0-inf, AUClast, Tlast, Clast, Cmax, CL/F, and Vz/F. A linear model was fitted to the log-transformed PK parameters with the hepatic function groups (normal, mild, moderate, and severe) as fixed effects. For this analysis, the mild, moderate, and severe groups were considered as the tests, while the normal group was the reference. The point estimate of the treatment difference and the corresponding 90% confidence intervals (CI) were calculated and anti-logged 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. Comparisons were performed between each hepatic dysfunction group and the normal liver function group.

Summary PK parameters were presented for metabolite BJB432. Summary of plasma protein binding was also presented by liver function group.

Baseline BSA and age were included in the primary analysis model. Results from the full model with all relevant covariates were reported.

For Tmax, point estimates and 90% CIs of the difference between test and reference were provided using non-parametric methods (Hodges-Lehmann estimate and Moses CI.

The assessment of safety was based mainly on the frequency of treatment-emergent adverse events and on the number of treatment-emergent laboratory values that fall outside of pre-determined ranges (CTCAE v.3.0 grading or normal ranges as appropriate). Other safety data (e.g., ECG, vital signs, and special tests) were considered as appropriate.

No interim analysis has been planned and performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Patient had documented diagnosis of advanced solid tumor for which no standard systemic therapy exist
- Patient had normal or abnormal hepatic function

- Patient had provided written informed consent prior to any screening procedures.

Exclusion criteria:

- Patient needing valproic acid for any medical condition during the study or within 5 days prior to first panobinostat dose
- Patient received prior treatment with DAC inhibitors including panobinostat
- Patient required treatment with warfarin that could not be switched to another anti-coagulant treatment prior to starting study drug
- Patient had encephalopathy
- Patient had ascites requiring intervention
- Female patient who was pregnant or breast feeding or with childbearing potential and not willing to use a double method of contraception up to 3 months after the end of the study treatment. Male patient who was not willing to use a barrier method of contraception up to 3 months after the end of the study treatment.

Participant Flow

Patient disposition, by NCI-CTEP hepatic function groups (Full analysis set)

Disposition	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=6) n (%)	Severe (N=1) n (%)	All Patients (N=25) n (%)
Primary reason for end of treatment					
Adverse Event(s)	1 (10.0)	1 (12.5)	1 (16.7)	1 (100.0)	4 (16.0)
Abnormal laboratory value(s)	0	0	0	0	0
Patient withdrew consent	0	2 (25.0)	1 (16.7)	0	3 (12.0)
Disease progression	9 (90.0)	5 (62.5)	4 (66.7)	0	18 (72.0)
Protocol deviation	0	0	0	0	0
Primary reason for study evaluation completion					
Patient withdrew consent	0	2 (25.0)	1 (16.7)	0	3 (12.0)
Lost to follow-up	1 (10.0)	0	0	1 (100.0)	2 (8.0)
Administrative problems	1 (10.0)	0	0	0	1 (4.0)
Death	2 (20.0)	2 (25.0)	2 (33.3)	0	6 (24.0)
Disease progression	6 (60.0)	4 (50.0)	2 (33.3)	0	12 (48.0)
F/u phase compl as per prot.	0	0	1 (16.7)	0	1 (4.0)

Baseline characteristics, by NCI-CTEP hepatic function groups (Full analysis set)

Demographic variable	Normal (N=10)	Mild (N=8)	Moderate (N=6)	Severe (N=1)	All patients (N=25)
Age (years)					
n	10	8	6	1	25
Mean	56.30	54.25	65.17	58.00	57.84

Demographic variable	Normal (N=10)	Mild (N=8)	Moderate (N=6)	Severe (N=1)	All patients (N=25)
SD	10.520	7.344	5.231		9.035
Median	52.00	54.00	65.00	58.00	58.00
Min	45.0	46.0	59.0	58.0	45.0
Max	76.0	67.0	74.0	58.0	76.0
Sex – n (%)					
Male	4 (40.0)	4 (50.0)	5 (83.3)	1 (100.0)	14 (56.0)
Female	6 (60.0)	4 (50.0)	1 (16.7)	0	11 (44.0)
Race – n (%)					
Caucasian	10 (100.0)	8 (100.0)	6 (100.0)	1 (100.0)	25 (100.0)
Ethnicity – n (%)					
Hispanic/Latino	2 (20.0)	2 (25.0)	0	0	4 (16.0)
Other	8 (80.0)	6 (75.0)	6 (100.0)	1 (100.0)	21 (84.0)
Weight (kg)					
n	10	8	6	1	25
Mean	72.87	82.14	88.70	74.40	79.70
SD	19.678	19.995	10.322		18.079
Median	69.20	83.15	89.10	74.40	81.90
Min	49.0	49.3	75.0	74.4	49.0
Max	112.8	109.3	101.0	74.4	112.8
Height (cm)					
n	10	7	6	1	24
Mean	165.30	173.86	178.83	174.00	171.54
SD	10.231	6.744	4.309		9.464
Median	166.50	171.00	180.00	174.00	171.50
Min	151.0	167.0	172.0	174.0	151.0
Max	184.0	183.0	183.0	174.0	184.0
Body mass index (kg/m^2)					
n	10	7	6	1	24
Mean	26.58	26.89	27.76	24.57	26.88
SD	6.507	6.765	3.332		5.603
Median	25.61	28.79	28.23	24.57	26.96
Min	19.5	17.5	22.6	24.6	17.5
Max	41.4	37.4	32.6	24.6	41.4
Body surface area (m2)					
n	10	7	6	1	24
Mean	1.82	1.97	2.10	1.90	1.93
SD	0.271	0.288	0.128		0.259
Median	1.75	2.02	2.11	1.90	1.98
Min	1.4	1.5	1.9	1.9	1.4
Max	2.3	2.3	2.2	1.9	2.3

Demographic variable	Normal (N=10)	Mild (N=8)	Moderate (N=6)	Severe (N=1)	All patients (N=25)
Baseline ECOG performance status – n (%)					
0	5 (50.0)	0	2 (33.3)	0	7 (28.0)
1	5 (50.0)	7 (87.5)	4 (66.7)	1 (100.0)	17 (68.0)
2	0	1 (12.5)	0	0	1 (4.0)

Outcome measures

Primary Outcome Result(s): PK results

Summary of panobinostat plasma PK parameters by NCI-CTEP hepatic function groups (PK set)

PK Parameter (unit)	Normal (N=10)	Mild (N=7)	Moderate (N=6)	Severe (N=1)
Tmax (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)
Cmax (ng/mL)	18.5 (81.18)	29.1 (57.3)	33.9 (50.9)	31.2 (NE)
AUC0-48 (ng*h/mL)	125.0 (70.3)	183.9 (54.2)	249.9 (43.2)	235.4 (NE)
AUC0-inf (ng*h/mL)	150.3 (72.3)	214.8 (56.3)	308.0 (44.2)	272.3 (NE)
AUClast (ng*h/mL)	140.5 (73.3)	204.3 (56.2)	284.9 (42.6)	263.9 (NE)
CL/F (L/h)	199.6 (72.3)	139.7 (56.3)	97.4 (44.2)	110.2 (NE)
Vz/F (L)	8295(54.7)	5297 (48.1)	4864 (35.1)	3157 (NE)
T1/2 (h)	28.8 (27.3)	26.3 (27.6)	34.6 (31.5)	19.9 (NE)
Clast (ng/mL)	0.24 (0.13- 0.42)	0.27 (0.11- 0.46)	0.52 (0.17- 0.61)	0.29 (0.3-0.3)
Tlast (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)

Values are geometric mean (%CV) except for Clast, Tmax, and Tlast (median; range)
NE: not estimable

Summary of statistical analysis of panobinostat PK parameters, by NCI-CTEP hepatic function groups (PK set)

					Treatment Comparison		
						90% CI	
PK Parameter (unit)	Treatment	n*	Adjusted Geo-mean	Comparison	Geo-mean Ratio	Lower	Upper
Tmax (h)	Normal	10	2.00				
	Mild	7	2.00	Mild - Normal	0	-1.03	1.03
	Moderate	6	2.00	Mod - Normal	0	-1.00	1.50
	Severe	1	2.00	Severe - Normal	0	-5.00	1.50
Cmax (ng/mL)	Normal	10	16.29				
	Mild	6	32.35	Mild: Normal	1.99	1.119	3.523
	Moderate	6	42.20	Mod: Normal	2.59	1.324	5.071
	Severe	1	29.91	Severe: Normal	1.84	0.613	5.498

PK Parameter (unit)	Treatment	n*	Adjusted Geo-mean	Comparison	Treatment Comparison		
						90% CI	
					Geo-mean Ratio	Lower	Upper
AUC0-48 (ng*h/mL)	Normal	10	125.40				
	Mild	6	183.66	Mild: Normal	1.46	0.837	2.562
	Moderate	6	239.17	Mod: Normal	1.91	0.991	3.670
	Severe	1	234.85	Severe: Normal	1.87	0.643	5.454
CL/F (mL/h)	Normal	10	197855.4				
	Mild	6	139809.9	Mild: Normal	0.71	0.398	1.253
	Moderate	6	102812.1	Mod: Normal	0.52	0.266	1.016
	Severe	1	110246.0	Severe: Normal	0.56	0.186	1.666
Vz/F (mL)	Normal	10	8331968				
	Mild	6	5379062	Mild: Normal	0.65	0.406	1.026
	Moderate	6	4988007	Mod: Normal	0.60	0.348	1.030
	Severe	1	3171250	Severe: Normal	0.38	0.157	0.923
AUC0-inf (ng*h/mL)	Normal	10	151.63				
	Mild	6	214.58	Mild: Normal	1.42	0.798	2.510
	Moderate	6	291.79	Mod: Normal	1.92	0.984	3.764
	Severe	1	272.12	Severe: Normal	1.79	0.600	5.367
T1/2 (h)	Normal	10	29.19				
	Mild	6	26.67	Mild: Normal	0.91	0.685	1.219
	Moderate	6	33.63	Mod: Normal	1.15	0.822	1.615
	Severe	1	19.94	Severe: Normal	0.68	0.393	1.186
AUClast (ng*h/mL)	Normal	10	141.63				
	Mild	6	204.12	Mild: Normal	1.44	0.812	2.557
	Moderate	6	269.91	Mod: Normal	1.91	0.974	3.730
	Severe	1	263.68	Severe: Normal	1.86	0.622	5.574

n* = number of patients with non-missing values.

Geo-mean = geometric mean. Geo-mean, Geo-mean ratio, and 90% CI are all determined from a linear model and back-transformed from log scale.

The model for T1/2, Vz/F, CL/F, AUC and Cmax is as follows: lnPK = group + age + BSA.

For Tmax, median is presented under ‘Adjusted Geo-mean’, Hodges-Lehmann estimate under ‘Geo-mean ratio’, and distribution free CI under 90% CI

Secondary Outcome Result(s): safety results

Adverse Events, regardless of study drug relationship, by SOC (occurring in at least 10% of patients) and by NCI-CTEP hepatic function group (Safety set)

Primary system organ class	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=6) n (%)	Severe (N=1) n (%)	All patients (N=25) n (%)
Total	10 (100.0)	8 (100.0)	6 (100.0)	1 (100.0)	25 (100.0)
Gastrointestinal disorders	10 (100.0)	8 (100.0)	5 (83.3)	0	23 (92.0)
General disorders and administration site conditions	10 (100.0)	6 (75.0)	6 (100.0)	0	22 (88.0)
Metabolism and nutrition disorders	8 (80.0)	6 (75.0)	6 (100.0)	0	20 (80.0)
Respiratory, thoracic and mediastinal disorders	7 (70.0)	3 (37.5)	3 (50.0)	0	13 (52.0)
Blood and lymphatic system disorders	6 (60.0)	2 (25.0)	4 (66.7)	0	12 (48.0)
Investigations	2 (20.0)	4 (50.0)	4 (66.7)	1 (100.0)	11 (44.0)
Infections and infestations	5 (50.0)	4 (50.0)	1 (16.7)	0	10 (40.0)
Nervous system disorders	4 (40.0)	3 (37.5)	3 (50.0)	0	10 (40.0)
Musculoskeletal and connective tissue disorders	3 (30.0)	2 (25.0)	4 (66.7)	0	9 (36.0)
Skin and subcutaneous tissue disorders	5 (50.0)	0	1 (16.7)	0	6 (24.0)
Vascular disorders	2 (20.0)	2 (25.0)	2 (33.3)	0	6 (24.0)
Psychiatric disorders	1 (10.0)	2 (25.0)	2 (33.3)	0	5 (20.0)
Renal and urinary disorders	1 (10.0)	2 (25.0)	2 (33.3)	0	5 (20.0)
Eye disorders	2 (20.0)	1 (12.5)	0	0	3 (12.0)
Reproductive system and breast disorders	1 (10.0)	2 (25.0)	0	0	3 (12.0)

Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse events, regardless of study drug relationship, by preferred term (occurring in at least 50% of patients) and by NCI-CTEP hepatic function groups (Safety set)

Preferred term	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=6) n (%)	Severe (N=1) n (%)	All patients (N=25) n (%)
Total	10 (100.0)	8 (100.0)	6 (100.0)	1 (100.0)	25 (100.0)
Fatigue	8 (80.0)	5 (62.5)	6 (100.0)	0	19 (76.0)
Nausea	8 (80.0)	7 (87.5)	4 (66.7)	0	19 (76.0)
Decreased appetite	6 (60.0)	6 (75.0)	5 (83.3)	0	17 (68.0)

Preferred term	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=6) n (%)	Severe (N=1) n (%)	All patients (N=25) n (%)
Vomiting	8 (80.0)	5 (62.5)	3 (50.0)	0	16 (64.0)
Diarrhoea	8 (80.0)	5 (62.5)	0	0	13 (52.0)
Oedema peripheral	4 (40.0)	1 (12.5)	5 (83.3)	0	10 (40.0)
Anaemia	2 (20.0)	2 (25.0)	4 (66.7)	0	8 (32.0)
Dyspnoea	4 (40.0)	2 (25.0)	2 (33.3)	0	8 (32.0)
Thrombocytopenia/ Platelet count decreased	5 (50.0)	2 (25.0)	6 (100.0)	0	13 (52.0)

Serious Adverse Events and Deaths

Deaths, other serious or clinically significant adverse events or related discontinuations, by NCI-CTEP hepatic function group (Safety set)

Serious or significant events	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=6) n (%)	Severe (N=1) n (%)	All patients (N=25) n (%)
All deaths	2 (20.0)	2 (25.0)	2 (33.3)	0	6 (24.0)
On treatment deaths	2 (20.0)	1 (12.5)	2 (33.3)	0	5 (20.0)
All SAEs	8 (80.0)	4 (50.0)	1 (16.7)	0	13 (52.0)
Study-drug-related SAEs	6 (60.0)	2 (25.0)	1 (16.7)	0	9 (36.0)
AEs leading to discontinuation	1 (10.0)	1 (12.5)	1 (16.7)	1 (100.0)	4 (16.0)
Clinically significant AEs	9 (90.0)	7 (87.5)	6 (100.0)	1 (100.0)	23 (92.0)

Except for 'all deaths' row, all other rows only include events happened on or after the first dose and up to 28 days after last dose of study drug.
Clinical significant/notable AEs defined as per clinical program-related criteria.

Other Relevant Findings

Grade 3/4 adverse events, regardless of study drug relationship, by primary SOC (occurring in at least 10% of patients) and by NCI-CTEP hepatic function group (Safety set)

Primary system organ class	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=6) n (%)	Severe (N=1) n (%)	All patients (N=25) n (%)
Total	10 (100.0)	6 (75.0)	6 (100.0)	1 (100.0)	23 (92.0)
Gastrointestinal disorders	6 (60.0)	5 (62.5)	1 (16.7)	0	12 (48.0)
General disorders and administration site conditions	6 (60.0)	4 (50.0)	2 (33.3)	0	12 (48.0)
Blood and lymphatic system disorders	4 (40.0)	0	2 (33.3)	0	6 (24.0)

Primary system organ class	Normal (N=10) n (%)	Mild (N=8) n (%)	Moderate (N=6) n (%)	Severe (N=1) n (%)	All patients (N=25) n (%)
Investigations	0	1 (12.5)	2 (33.3)	1 (100.0)	4 (16.0)

An effect of altered liver function on PK was clearly observed. However the clinical relevance of liver-function-related PK changes could not be adequately established in regard to safety, as increased exposures of panobinostat did not lead to corresponding increases in the main toxicities, thrombocytopenia and QTc prolongation.The relationship between exposures and unexpected drug-related SAE could not be assessed as only one male patient, 61 years old, with moderate hepatic impairment who experienced grade 3 skin vasculitis leading to permanent treatment discontinuation. His exposure was well below the exposures of patients in his organ dysfunction group.

Date of Clinical Trial Report

15-Oct-2013

Date Inclusion on Novartis Clinical Trial Results Database

18-Nov-2013

Date of Latest Update