Sponsor Novartis
Generic Drug Name Panobinostat (LBH589)
Therapeutic Area of Trial Advanced solid tumors
Approved Indication Investigational
Study Number CLBH589A1101
Title A phase IA, dose-escalating study of LBH589 administered intravenously in Japanese adult patients with advanced solid tumors
Phase of Development Phase I
Study Start/End Dates 10 Jul 2008 to 04 Dec 2009
Study Design/Methodology This study was an open-label, multicenter Phase IA dose-escalation study of LBH589 administered intravenously once daily on day 1 and 8 of a 21-day cycle. A standard 3+3 method was used for dose level selection and evaluation of safety. Patients in each cohort were to be treated with LBH589 according to the provisional dose levels listed below: Cohort 1: 10 mg/m^2 Cohort 2: 15 mg/m^2 Cohort 3: 20 mg/m^2
Centers 3 centers in Japan

Publication

None

Objectives

Primary objective(s)

- To characterize the safety and tolerability of LBH589, including DLT and MTD, as a single agent when administered as an intravenous infusion to adult patients with advanced solid tumors whose disease has progressed despite available standard therapies or for which no standard therapy exists

Secondary objective(s)

- To characterize the pharmacokinetics of LBH589
- To evaluate preliminary antitumor activity of LBH589 in patients with advanced solid tumors

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

LBH589 was administered by a 30-minute IV infusion on days 1 and 8 of each 21-day cycle. The starting dose of this study was set to be 10 mg/m^2.

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

None

Criteria for Evaluation

Safety

Incidence of dose limiting toxicities (DLTs) was the primary variable for safety and tolerability assessment. Safety assessments consisted of adverse events (AEs), laboratory test data (hematology, blood chemistry, thyroid function, and urine), vital signs, physical examination, and ECGs. Other cardiac assessments [including cardiac enzymes; cardiac troponin, creatine phosphokinase (CK), and the MB isoenzyme of CK (CK-MB)] and chest x-rays were repeated as clinically indicated.

Efficacy

Tumor responses were evaluated by RECIST criteria.

PK

PK profiles were evaluated on days 1 and 8 in cycle 1. Plasma LBH589 concentrations were determined by a validated LC-MS/MS method. The Limit of quantification (LOQ) was 0.500 ng/mL. PK parameters were calculated by non-compartment methods.

Statistical Methods

Safety: The assessment of safety was based on the type and frequency of adverse events, and on the number of patients whose CTC grade was worsened compared to the baseline grade, for

the safety set. Estimation of the maximum tolerated dose (MTD) was based upon the observed DLTs in Cycle 1 for patients in the MTD-determining set.

Efficacy: Best overall response in each patient was evaluated as Complete response (CR), Partial response (PR), Progressive disease (PD), Stable disease (SD), or Unknown (UNK). Overall confirmed response (CR + PR) was evaluated according to RECIST and summarized on the full analysis set (FAS).

PK: All PK analyses except listing of plasma concentration were performed on the PK set. For the listings of plasma LBH589 concentrations, the safety set was used instead. Descriptive statistics (mean, geometric mean, SD, median, range) were performed on PK parameters for LBH589 by scheduled time-point (day 1 and day 8) and initial dose cohort.

Study Population: Inclusion/Exclusion Criteria

Inclusion criteria

- Patients with histologically-confirmed advanced solid tumors whose disease had progressed despite available standard therapies or for which no standard therapy existed; age ≥ 20 years old, ECOG Performance Status of ≤ 2, life expectancy of ≥ 12 weeks
- At least one measurable or non-measurable but evaluable lesion as defined by modified RECIST criteria for solid tumors

Exclusion criteria

- Patients with evidence of CNS tumor or metastasis
- Patients with pleural effusion and/or ascites to be drained
- Patients with any peripheral neuropathy ≥ CTCAE grade 2
- Impaired cardiac function, acute or chronic liver or renal disease, other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes or systemic infection) that could cause unacceptable safety risks or compromise compliance with the protocol
- Patients who underwent major surgery ≤ 4 weeks prior to starting study drug or received chemotherapy ≤ 4 weeks, immunotherapy ≤ 2 weeks, any investigational drug ≤ 4 weeks, wide field radiotherapy ≤ 4 weeks or limited field radiation ≤ 2 weeks prior to starting study drug or who had not recovered from side effects of such therapy.
- Patients with hypooncotic dehydration (contraindication of 5% Dextrose in water)

Number of Subjects

Patient disposition (FAS)

	10 mg/m^2 N = 3		15 mg/m^2 N = 3		20 mg/m^2 N = 8		All N = 14	
	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated								
Treated	3	(100.0)	3	(100.0)	8	(100.0)	14	(100.0)
Discontinued	3	(100.0)	3	(100.0)	8	(100.0)	14	(100.0)
Primary reason for discontinuation								
Adverse Event(s)	0	(0.0)	0	(0.0)	2	(25.0)	2	(14.3)
Patient withdrew consent	0	(0.0)	0	(0.0)	2	(25.0)	2	(14.3)
Disease progression	3	(100.0)	3	(100.0)	4	(50.0)	10	(71.4)

Demographic and Background Characteristics

Demographic summary by dose cohort (FAS)

Demographic variable	10 mg/m^2 N = 3	15 mg/m^2 N = 3	20 mg/m^2 N = 8	All N = 14
Sex -n (%)				
Female	2 (66.7)	1 (33.3)	2 (25.0)	5 (35.7)
Male	1 (33.3)	2 (66.7)	6 (75.0)	9 (64.3)
Age (Years)				
mean	55.3	66.3	63.8	62.5
s.d.	6.51	6.81	10.65	9.53
median	55.0	64.0	67.0	63.0
minimum	49.0	61.0	43.0	43.0
maximum	62.0	74.0	75.0	75.0
Age category (Years) -n (%)				
< 65	3 (100.0)	2 (66.7)	3 (37.5)	8 (57.1)
≥ 65	0	1 (33.3)	5 (62.5)	6 (42.9)
Race -n (%)				
Oriental	3 (100.0)	3 (100.0)	8 (100.0)	14 (100.0)
Weight (kg)				
mean	48.3	57.7	54.8	54.0
s.d.	4.49	5.46	9.52	8.22
median	47.6	56.8	52.6	53.0
minimum	44.2	52.8	44.9	44.2
maximum	53.1	63.6	71.2	71.2
Height (cm)				
mean	158.2	160.3	163.2	161.5
s.d.	4.31	8.43	6.01	6.15
median	159.0	162.6	162.4	161.6
minimum	153.5	151.0	155.6	151.0

maximum	162.0	167.4	170.3	170.3
Body surface area (m^2)				
mean	1.5	1.6	1.6	1.6
s.d.	0.04	0.12	0.15	0.13
median	1.5	1.6	1.6	1.5
minimum	1.4	1.5	1.4	1.4
maximum	1.5	1.7	1.8	1.8

Primary Objective Result(s)

Maximum tolerated dose (MTD)

DLTs were assessed in 12 patients for the MTD–determining population: each 3 patients in the 10 mg/m^2 and 15 mg/m^2 cohort, and 6 patients in the 20 mg/m^2 cohort. One out of 6 patients in the 20 mg/m^2 cohort experienced a DLT of grade 3 γ-GTP increased on Day 3 in Cycle 1.

By the time the 20 mg/m^2 cohort was completed, it was clear from another study CLBH589A2101 that 25 mg/m^2 was not a tolerable dose. Based on the overall information regarding safety, the 20 mg/m^2 was identified as tolerable when given on Days 1 and 8 of a 21-day treatment cycle. Therefore, the decision was made to declare 20 mg/m^2 the MTD in Japanese patients without testing a higher dose.

Secondary Objective Result(s)

Overall confirmed response rate by dose cohort (FAS)

	10 mg/m^2 N = 3		15 mg/m^2 N = 3		20 mg/m^2 N = 8		All N = 14	
Overall confirmed response	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Complete response (CR)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Partial response (PR)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Stable disease (SD)	2	(66.7)	1	(33.3)	4	(50.0)	7	(50.0)
Progressive disease (PD)	1	(33.3)	1	(33.3)	1	(12.5)	3	(21.4)
Unknown (UNK)	0	(0.0)	1	(33.3)	3	(37.5)	4	(28.6)
Overall response rate (CR/PR)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Summary of pharmacokinetic parameters by dose cohort (PK set)

Dose		Cmax (ng/mL)	AUC0-168h (ng·hr/mL)	AUCinf (ng·hr/mL)	CL (L/hr)	T1/2 (hr)
10 mg/m^2	Day 1 (N = 3)	272.0±42.58	273.2±36.50	273.7±36.49	54.1±5.61	16.8±1.17
	Day 8 (N = 3)	317.7±125.90	333.2±78.36	309.3±67.50	48.8±9.54	17.4±4.62
15 mg/m^2	Day 1 (N = 3)	496.0±226. 8	680.3±431.10	433.6±68.44[a]	53.7±5.54[a]	16.9±2.97[a]
	Day 8 (N = 3)	308.7±158.53	503.0±156.96	441.3±140.24	57.7±15.91	17.9±1.26
20 mg/m^2	Day 1 (N = 8)	492.8±147.80	605.1±132.14	606.8±132.20	54.0±12.78	18.5±2.12
	Day 8 (N = 5)	526.8±101.77	755.6±225.33	791.4±235.52	42.0±14.06	36.9±19.05

Mean ± SD except for Tmax of median (range)

a: N=2

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class and preferred term (> 20% for all patients) (SAF)

	10 mg/m^2 N = 3		15 mg/m^2 N = 3		20 mg/m^2 N = 8		All N = 14	
System organ class	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Preferred term	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Patients with AE(s)	3 (100.0)	1 (33.3)	3 (100.0)	3 (100.0)	8 (100.0)	8 (100.0)	14 (100.0)	12 (85.7)
Blood and lymphatic system disorders	3 (100.0)	1 (33.3)	3 (100.0)	2 (66.7)	8 (100.0)	7 (87.5)	14 (100.0)	10 (71.4)
Thrombocytopenia	3 (100.0)	1 (33.3)	3 (100.0)	2 (66.7)	8 (100.0)	5 (62.5)	14 (100.0)	8 (57.1)
Leukopenia	3(100.0)	0	1 (33.3)	1 (33.3)	5 (62.5)	2 (25.0)	9 (64.3)	3(21.4)
Neutropenia	2 (66.7)	0	1 (33.3)	1 (33.3)	5 (62.5)	3 (37.5)	8 (57.1)	4(28.6)
Gastrointestinal disorders	2 (66.7)	0	3(100.0)	0	6 (75.0)	0	11(78.6)	0
Nausea	1 (33.3)	0	2 (66.7)	0	4 (50.0)	0	7 (50.0)	0
Stomatitis	2 (66.7)	0	1 (33.3)	0	3 (37.5)	0	6 (42.9)	0
Vomiting	1 (33.3)	0	1 (33.3)	0	3 (37.5)	0	5 (35.7)	0
Constipation	1 (33.3)	0	0	0	3 (37.5)	0	4 (28.6)	0
Diarrhoea	1 (33.3)	0	1 (33.3)	0	2 (25.0)	0	4 (28.6)	0
General disorders and administration site conditions	2 (66.7)	0	2 (66.7)	1 (33.3)	5 (62.5)	1 (12.5)	9 (64.3)	2 (14.3)
Fatigue	2 (66.7)	0	2 (66.7)	1 (33.3)	3 (37.5)	1 (12.5)	7 (50.0)	2(14.3)
Pyrexia	0	0	1 (33.3)	0	4 (50.0)	0	5 (35.7)	0
Investigations	1 (33.3)	0	1 (33.3)	0	1 (12.5)	0	3 (21.4)	0
Weight decreased	1 (33.3)	0	1 (33.3)	0	1 (12.5)	0	3 (21.4)	0
Metabolism and nutrition disorders	1 (33.3)	0	3(100.0)	1 (33.3)	6 (75.0)	0	10(71.4)	1 (7.1)
Decreased appetite	1 (33.3)	0	2 (66.7)	1 (33.3)	5 (62.5)	0	8 (57.1)	1 (7.1)
Hypoalbuminaemia	1 (33.3)	0	3(100.0)	0	2 (25.0)	0	6 (42.9)	0
Nervous system disorders	2 (66.7)	0	1 (33.3)	0	1 (12.5)	0	4 (28.6)	0
Dysgeusia	2 (66.7)	0	1 (33.3)	0	1 (12.5)	0	4 (28.6)	0
Skin and subcutaneous tissue disorders	2 (66.7)	0	0	0	3 (37.5)	0	5 (35.7)	0
Rash	2 (66.7)	0	0	0	3 (37.5)	0	5 (35.7)	0

A patient with multiple occurrences of an AE under any group is counted only once in the AE category.

A patient with multiple severity ratings for an AE while on a treatment, is only counted under the maximum rating

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending order of frequency in the All patients column

Frequently observed AEs

The most commonly affected primary SOCs were blood and lymphatic system disorders, gastrointestinal disorders, and metabolism and nutrition disorders. The most frequently occurring AEs were thrombocytopenia (100%), leukopenia (64.3%), neutropenia and decreased appetite (57.1% each), nausea and fatigue (50.0% each).

Serious Adverse Events and Deaths

No patients died during the study. One patient in the 15 mg/m^2 cohort and 2 patients in the 20 mg/m^2 cohort experienced SAE.

Date of Clinical Trial Report

22 Dec 2010 (content final)

Date Inclusion on Novartis Clinical Trial Results Database

5 Aug 2011

Date of Latest Update