Sponsor

Novartis

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Hormone refractory prostate cancer

Approved Indication

Investigational

Study Number

CLBH589B2105

Title

A phase IA/IB, two arm, multi-center, open-label, dose escalation study of oral LBH589 alone and in combination with IV docetaxel (Taxotere®) and oral prednisone in hormone refractory prostate cancer (HRPC).

Phase of Development

IA/IB

Study Start/End Dates

09 May 2006 to 25 Jul 2008

Study Design/Methodology

This was a two-arm, open-label, multicenter phase IA/IB study of LBH589 (oral formulation) alone and in combination with docetaxel in patients with progressing HRPC. This study was designed to determine the MTD (maximum tolerable dose) or OBD (optimum biologic dose), if defined, of LBH589 as a single agent (Arm I) and in combination with docetaxel 75mg/m2 i.v. and oral prednisone 5 mg b.i.d. (Arm II), and to characterize the safety, tolerability, biologic activity, and pharmacokinetic profile.

Centres

5 centers in USA

Publication

Dana Rathkopf, Bryan Wong et al.(2010) A phase I study of oral panobinostat alone and in

combination with docetaxel in patients with castration-resistant prostate cancer Cancer Chemotherapy and Pharmacology, Published Online 09 Mar 2010, DOI 10.1007/s00280-010-1289-x

Objectives

Primary objective(s)

- To determine the maximum-tolerated dose (MTD) and dose-limiting toxicity (DLT) of escalating doses of LBH589 in adult men with HRPC.
- To determine the MTD and DLT of escalating doses of LBH589 in combination with a standard dose of docetaxel q3wks and daily Prednisone® in adult men with HRPC.

Secondary objective(s)

- To characterize the safety and tolerability of LBH589 alone and in combination with docetaxel and Prednisone® including acute and chronic toxicities.
- To characterize the single-dose and multidose pharmacokinetic (PK) profiles of LBH589 alone and in combination with docetaxel and Prednisone®. To characterize the PK profiles of docetaxel alone and in combination with LBH589.

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

LBH589 5 mg and 20 mg hard gelatin capsules were administered once a day orally on Monday, Wednesday and Friday (MWF) for 2 weeks with one week off, as part of a 3 week (21 day) treatment cycle.

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

None

Criteria for Evaluation

Efficacy variables

- All potential sites of tumor lesions were assessed at baseline by radiologic techniques and physical examination.
- Soft tissue lesions were measured by response evaluation criteria in solid tumors (RECIST).
- Bone scintigraphy was used to assess for new bony lesions.
- Post-treatment changes of PSA were explored descriptively. PSA was not used as an outcome measure to define treatment responders or disease progression, because preclinical studies indicate that HDAC inhibitors may upregulate PSA independent of its effect on tumor growth.

Safety and tolerability

- Recording and monitoring all adverse events (AEs), including serious adverse events (SAEs), and the regular monitoring of hematology and blood chemistry values.
- Additional assessments included thyroid function, and cardiac enzymes, regular monitoring of vital signs, physical examination status, body weight, electrocardiograms (ECGs).

Pharmacology

Pharmacokinetics

- Single dose and steady state pharmacokinetics (PK) of LBH589 as a single agent were evaluated in Arm I. LBH589 PK in combination with and without docetaxel was assessed in Arm II.

Statistical Methods

Descriptive summaries or listings of clinical data as well as pharmacokinetic data were generated. No inferential analyses were performed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria

- Histologically documented adenocarcinoma of the prostate.
- Arm I (LBH 589 alone):
  - Dose Escalation Phase - HRPC patients who had received at least one chemotherapy regime including docetaxel and were no longer candidates to receive further chemotherapy with dcetaxel.
  - Dose Expansion Phase - HRPC patients who had received at least one regimen of docetaxel and were not scheduled for further therapy with docetaxel.
- Arm II (LBH 589 and docetaxel/prednisone):
  - Dose Escalation Phase - HRPC patients who had not received prior cytotoxic chemother-

apy for prostate cancer and also patients who had relapsed after prior docetaxel therapy and were candidates for subsequent docetaxel and prednisone therapy.

- Dose Expansion Phase - HRPC patients who had not received prior cytotoxic chemotherapy.

- Clinically progressing hormone-refractory disease, as documented by one or more of the following:
  - Two documented consecutive increases in PSA over a previous reference value (first increase at least 1 week after reference value). The second documented increase must have been = 1 week after the first documented increase. If the second increase was not above the first increase than a third PSA must have been provided. The third PSA should have been greater than the first documented increase. The increasing PSA should have had a value of at least 5 ng/mL.
  - New lesions on bone scan (progressive bone disease).
  - Clinically significant increase in unidimensionally measurable disease of tumor soft tissue lesions (e.g. change in lymph node size).
- Patients receiving antiandrogen treatment, as first line, must have demonstrated no decrease in PSA values on at least 2 occasions = 1 week apart after antiandrogen withdrawal. Flutamide must have been discontinued for = 4 weeks, and bicalutamide, megestrol acetate, cyproterone acetate, or nilutamide must have been discontinued for = 6 weeks prior to study entry.
- Patients must have had metastatic disease with at least one measurable soft tissue lesion that could be assessed by CT or MRI and/or detectable lesion(s) on bone scintigraphy scan. Patients with only elevated PSA levels were not eligible for entry.
- Patients scheduled for FDHT PET should have had uptake of the tracer in at least one lesion (tumor-to-muscle ratio >2) in the baseline FDHT PET scan in order to be eligible for the post treatment FDHT PET scans.
- Patients who have undergone medical castration must have continued LHRH agonist or antagonist therapy during study treatment.
- Patients who had not received prior surgical castration, must have had a serum testosterone level < 50 ng/mL with continuation of gonadotropin-releasing hormone agonist/antagonist.
- No symptomatic pleural effusion, t third space fluid accumulation (e.g. ascites) or concurrent brain metastases.
- Biochemistry.
  - Total calcium (corrected for serum albumin) = the lower limit of normal or correctable with supplements.
  - Magnesium, potassium and phosphorus = the lower limit of normal or correctable with supplements.
  - Serum creatinine = 1.5 x ULN or 24-hour creatinine clearance = 50 ml/min.
  - Serum amylase = 1.5 x ULN and serum lipase = 1.5 x ULN.
- Arm I.
  - Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) = 2.5 x ULN or = 5.0 x ULN if hepatic involvement was present. Serum bilirubin = 1.5 x

ULN.

- Arm II.
  - Aspartate aminotransferase (AST/SGOT) and alanine aminotransferase (ALT/SGPT) = 1.5 x ULN. Serum bilirubin = 1.5 x ULN
- Thyroid function
  - Clinically Euthyroid (hypothyroidism correctable with supplements was allowed)
- Hematology:
  - ANC = 1500/mm3.
  - Platelet count = 100,000/mm3.
  - Hemoglobin = 8 g/dL.
- Patients must have been able to provide written informed consent
- Life expectancy = 12 weeks

Exclusion criteria

- Patients who were less then 3 weeks post radiotherapy. Patients must have recovered from prior radiotherapy.
- Pathologic long-bone fractures (unless surgically stabilized), imminent pathologic longbone fracture (cortical erosion on radiography > 50%), or spinal cord compression.
- Patients who had received prior radiotherapy to = 30% of the bone marrow.
- Patients who had received prior treatment with radioactive bone seeking agents (e.g. Samarium Sm 153 lexidronam (Quadramet), Strontium-89 Chloride injection (Metastron).
- Peripheral neuropathy (> Grade 1).
- Patients with a history of hypersensitivity reaction to docetaxel or other drugs formulated with polysorbate 80 (Arm II only).
- Patients with unresolved diarrhea = CTCAE grade 1.
- Impaired cardiac function, including any one of the following:
  - Cardiac - LVEF < 45% as determined by ECHO.
  - Complete Left Bundle Branch Block or obligate use of a cardiac pacemaker or congenital long QT syndrome or history or presence of ventricular tachyarrhythmias or clinically significant resting bradycardia (< 50 beats per minute) or QTcF > 480 msec on screening ECG or Right Bundle Branch block + left anterior hemiblock (bifasicular block).
  - Presence of unstable atrial fibrillation (ventricular response rate > 100 bpm). Patients with stable atrial fibrillation were allowed in the study provided they did not meet the other cardiac exclusion criteria.
  - Angina pectoris or acute mycocardial infarction = 3 months prior to starting study drug.
  - Other clinically significant heart disease (e.g. congestive heart failure, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).
- Impairment of gastrointestinal (GI) function or GI disease that may have significantly altered the absorption of oral LBH589 (e.g. ulcerative diseases, uncontrolled nausea, vomiting, malabsorption syndrome, or small bowel resection).

- Use of therapeutic androgens.
- Acute or chronic liver disease, renal disease.
- Other concurrent severe and/or uncontrolled medical conditions (e.g. uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease) that could have caused unacceptable safety risks or compromise compliance with the protocol.
- The medications having a relative risk of prolonging the QT interval or inducing Torsades de Pointes.
- Patients who were currently receiving treatment with any of the CYP3A4 inhibitors and the treatment could not be discontinued or switched to a different medication prior to starting study drug.
- Treatment with any hematopoietic colony-stimulating growth factors (e.g. G-CSF, GMCSF) = 2 weeks prior to starting study drug. Erythropoietin or darbepoetin therapy, if initiated before enrollment, may have been continued.
- Treatment with therapeutic doses of sodium warfarin (Coumadin). Low doses of Coumadin (e.g. = 2 mg/day) for line patency was allowable
- Patients who had received chemotherapy = 2 weeks (6 weeks for nitrosourea or mitomycin-C) prior to starting study drug or who had not recovered from side effects of such therapy.
- Patients who had received biologic (e.g. bortezomib, thalidomide, lenalidomide) therapy or immunotherapy = 2 weeks prior to starting study treatment or who had not recoveredfrom side effects of such therapy.
- Patients who had received any investigational drugs = 5 half lives prior to starting study drug or who had not recovered from side effects of such therapy.
- Patients who had received vaccine therapy = 2 weeks prior to starting study treatment or who had not recovered from side effects of such therapy.
- Patients who had undergone major surgery = 2 weeks prior to starting study drug or who had not recovered from side effects of such therapy.
- All sexually active male patients or their partners must have agreed to use adequate contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermacide or vasectomy) throughout the study.
- Known diagnosis of HIV infection (HIV testing was not mandatory).
- Patients with a history of another primary malignancy that was currently clinically significant or currently required active intervention.
- Current history of alcohol or drug abuse.
- Mental impairment limiting the ability to comply with study requirements.
- Patients with the inability to lie flat on the PET scanner table for approximately one hour.

Number of Subjects

Patient disposition, by treatment group (Full analysis set)

Disposition	LBH589 (20 mg) N=8 n (%)	LBH589 (15 mg) + docetaxel + prednisone N=8 n (%)
Enrolled*	8 (100.0)	8 (100.0)
Discontinued study**	8 (100.0)	8 (100.0)
Primary reason for end of treatment		
Adverse event(s)	4 (50.0)	3 (37.5)
Patient withdrew consent	0 (0.0)	2 (25.0)
Administrative problems	0 (0.0)	1 (12.5)
Disease progression	4 (50.0)	2 (25.0)

* Treated patients

** Patients who completed End of Treatment CRF page

Demographic and Background Characteristics

Demographic summary and baseline disease characteristics, by treatment group (Full analysis set)

Demographic Variable	LBH589 (20 mg) N=8	LBH589 (15 mg) + docetaxel + prednisone N=8
Baseline age (years)		
n	8	8
Mean	68.6	65.6
SD	5.88	6.57
Median	68.0	66.5
Minimum	60.0	53.0
Maximum	80.0	72.0
Baseline age (years) category-n (%)		
<65	2 (25.0)	3 (37.5)
=65	6 (75.0)	5 (62.5)
Race - n (%)		
Caucasian	8 (100.0)	8 (100.0)
Baseline weight (kg)		
n	8	8
Mean	89.0	86.2
SD	18.08	10.94
Median	88.5	81.5
Minimum	60.3	75.5

Maximum	117.9	103.5
WHO performance status1 - n (%)		
Grade 0	3 (37.5)	2 (25.0)
Grade 1	4 (50.0)	6 (75.0)
Grade 2	1 (12.5)	0 (0.0)
Source of subject referral - n (%)		
Physician referral	8 (100.0)	8 (100.0)

WHO performance status:

Grade 0: Fully active, able to carry on all pre-disease performance without restriction.

Grade 1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.

Grade 2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

Grade 3: Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

Grade 4: Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

Primary Objective Result(s)

Dose-limiting toxicities (DLT)

Two patients experienced dose-limiting toxicities (DLT) in cycle 1. In the LBH589 group, one patient experienced a worsening of shortness of breath. One patient in the LBH589 + docetaxel + prednisone group experienced Grade 3 neutropenia for more than 7 consecutive days.

Secondary Objective Result(s)

Best overall response by investigators and by calculation based on RECIST, by treatment group (Full analysis set)

	LBH589(20 mg) N=8 n (%)	LBH589(15 mg) + docetaxel + prednisone N=8 n (%)
Best overall response (by investigator)		
Partial response	0 (0.0)	2 (25.0)
Progressive disease	5 (62.5)	1 (12.5)
Stable disease	1 (12.5)	4 (50.0)
Unknown	2 (25.0)	1 (12.5)
Best overall response (calculated by RECIST)		
Partial response	0 (0.0)	3 (37.5)
Progressive disease	5 (62.5)	1 (12.5)
Stable disease	0 (0.0)	2 (25.0)
Unknown	3 (37.5)	2 (25.0)

PK parameters of LBH589 (Arm I) following single oral dose of 20 mg LBH589 (cycle 1 day 1) (PK set Arm I)

Statistics	AUC_{0-24} (ng*h/mL)	AUC_{0-inf} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)	$T_{1/2}$ (h)	Cl/F (L/h)	Vz/F (L)

20 mg/day (cycle 1 day 1)						
Mean 81.2	134.3	14.3	-	14.6	188.2	3260.7
(SD) (37.38)	(69.10)	(7.42)		(7.07)	(103.50)	(578.84)
CV% mean 46.1	51.5	51.8	-	48.5	55.0	17.8
Median 66.5	137.5	14.0	1.5	13.4	168.7	3486.4
Min - Max 42.0-134.0	64.0-198.0	5.0-26.1	0.5-3.0	7.7-24.0	101.0-314.3	2402.1-3667.8
n 6	4	8	8	4	4	4

PK parameters for oral LBH589 following a 15 mg dose +75 mg/m2 docetaxel (day 1 Arm II) and for oral LBH589 given alone at 15 mg (day 12 Arm II)

Statistics	AUC_{0-24} (ng*h/mL)	AUC_{0-inf} (ng*h/mL)	C_{max} (ng/mL)	T_{max} (h)
15 mg/day LBH589 (Cycle 1 Day 1)				
Mean (SD)	65.3 (19.22)	68.7 (18.15)	11.8 (11.15)	-
CV% mean	29.5	26.4	94.5	-
Median	66.5	66.0	5.6	1.0
Min -Max	43.0-85.0	52.0-88.0	3.4-33.7	0.5-4.0
n	4	3	7	7
15 mg/day LBH589 (Cycle 4 Day 12)				
Mean (SD)	96.0	115.0	5.1 (4.61)	-
CV% mean	-	-	91.4	-
Median	96.0	115.0	3.1	1.5
Min -Max	96.0-96.0	115.0-115.0	2.2-11.9	1.0-2.9
n	1	1	4	4

Safety Results

Adverse events, regardless of study drug relationship, by primary system organ class and treatment group (Safety set)

Primary system organ class	LBH589 (20 mg) N=8 n (%)		LBH589 (15 mg) + docetaxel + prednisone N=8 n (%)	
	Any grade	Grade 3/4	Any grade	Grade 3/4
-Any primary system organ class	8 (100.0)	5 (62.5)	8 (100.0)	8 (100.0)
Gastrointestinal disorders	8 (100.0)	1 (12.5)	7 (87.5)	1 (12.5)
General disorders and administration site conditions	5 (62.5)	0 (0.0)	5 (62.5)	2 (25.0)
Blood and lymphatic system disorders	5 (62.5)	0 (0.0)	8 (100.0)	7 (87.5)
Investigations	5 (62.5)	2 (25.0)	3 (37.5)	0 (0.0)
Metabolism and nutrition disorders	5 (62.5)	0 (0.0)	6 (75.0)	2 (25.0)
Renal and urinary disorders	4 (50.0)	2 (25.0)	3 (37.5)	0 (0.0)
Musculoskeletal and connective tissue disorders	3 (37.5)	0 (0.0)	4 (50.0)	1 (12.5)
Respiratory, thoracic and mediastinal disorders	3 (37.5)	1 (12.5)	5 (62.5)	0 (0.0)
Infections and infestations	2 (25.0)	2 (25.0)	3 (37.5)	1 (12.5)
Nervous system disorders	2 (25.0)	1 (12.5)	5 (62.5)	0 (0.0)
Psychiatric disorders	2 (25.0)	0 (0.0)	2 (25.0)	0 (0.0)
Cardiac disorders	1 (12.5)	1 (12.5)	0 (0.0)	0 (0.0)
Endocrine disorders	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)
Injury, poisoning and procedural complications	1 (12.5)	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	1 (12.5)	0 (0.0)	1 (12.5)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (12.5)	0 (0.0)	3 (37.5)	0 (0.0)
Vascular disorders	1 (12.5)	1 (12.5)	1 (12.5)	0 (0.0)
Eye disorders	0 (0.0)	0 (0.0)	3 (37.5)	0 (0.0)

Adverse events (at least 25% of any group), suspected to be related to study drug, by preferred term and treatment group (Safety set)

	LBH589 (20 mg) N=8 n (%)		LBH589 (15 mg) + docetaxel + prednisone N=8 n (%)	
Preferred term	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
Total	8 (100.0)	3 (37.5)	8 (100.0)	5 (62.5)
Nausea	6 (75.0)	1 (12.5)	5 (62.5)	0 (0.0)
Diarrhoea	4 (50.0)	1 (12.5)	3 (37.5)	0 (0.0)
Thrombocytopenia	4 (50.0)	0 (0.0)	1 (12.5)	0 (0.0)
Anorexia	3 (37.5)	0 (0.0)	1 (12.5)	0 (0.0)
Fatigue	3 (37.5)	0 (0.0)	4 (50.0)	2 (25.0)
Anaemia	2 (25.0)	0 (0.0)	4 (50.0)	1 (12.5)
Vomiting	2 (25.0)	0 (0.0)	3 (37.5)	0 (0.0)
Constipation	1 (12.5)	0 (0.0)	2 (25.0)	0 (0.0)
Leukopenia	1 (12.5)	0 (0.0)	2 (25.0)	2 (25.0)
Neutropenia	1 (12.5)	0 (0.0)	4 (50.0)	3 (37.5)
Decreased appetite	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)
Hyperglycaemia	0 (0.0)	0 (0.0)	2 (25.0)	2 (25.0)
Neuropathy peripheral	0 (0.0)	0 (0.0)	2 (25.0)	0 (0.0)

Deaths, other serious or clinically significant adverse events or related discontinuations, by treatment group (Safety set)

	LBH589 (20 mg) N=8 n (%)	LBH589 (15 mg) + docetaxel + prednisone N=8 n (%)
Patients with AE(s)*	8 (100.0)	8 (100.0)
Serious or other significant event		
Deaths (during study)**	0 (0.0)	0 (0.0)
All deaths***	4 (50.0)	1 (12.5)
All SAEs	4 (50.0)	5 (62.5)
Study-drug-related SAEs	3 (37.5)	1 (12.5)
AEs leading to discontinuation****	4 (50.0)	3 (37.5)

Note serious or other significant event categories are not mutually exclusive and the same patient may be counted in multiple categories.

* AEs (including SAEs and AEs leading to discontinuation) that occurred on treatment and up to 28 days after the last dose of study drug

** deaths that occurred on treatment and up to 28 days after the last dose of study drug

*** includes deaths as reported in Survival CRF page. Note that survival follow-up occurred every 3 months until the time at which all patients who received study drug had completed =4 cycles of study treatment. No death occurred during the study treatment period.

**** as reported in AE CRF page
Date of Clinical Trial Report 30 Jan 2009
Date Inclusion on Novartis Clinical Trial Results Database 21 April 2010
Date of Latest Update