Sponsor Novartis
Generic Drug Name Panobinostat
Therapeutic Area of Trial Prostate cancer
Approved Indication Investigational drug
Protocol Number CLBH589C2205
Title An open label, single arm, Phase 1b dose finding study of iv panobinostat (LBH589) with docetaxel & prednisone in patients with hormone refractory prostate cancer (HRPC).
Phase of Development Phase 1b
Study Start/End Dates 08-Feb-2008 (first patient first visit) to 20-Jan-2012 (last patient last visit)
Study Design/Methodology The study evaluated escalating doses of iv panobinostat administered on Day 1 and 8 in combination with iv docetaxel (75 mg/m^2) on Day 1 and daily oral prednisone (5 mg twice daily) in treatment cycles every 21 days.
Centres The study was conducted at nine sites in two countries (United States and Canada).
Publication None

Outcome measures

Primary outcome measures

The primary outcome measure was to determine the maximum tolerated dose (MTD) and any associated dose-limiting toxicities (DLTs) of panobinostat in combination with docetaxel and prednisone in HRPC patients.

Secondary outcome measures

- Efficacy: Tumor response to treatment using modified RECIST criteria, PSA response according to Prostate Cancer Working Group (PCWG) recommendations.
- Safety: Adverse events (AEs), serious adverse events (SAEs), laboratory tests, vital signs, physical examination, body weight, ECOG performance status; and serial ECGs monitoring.
- Pharmacokinetics (PK): PK parameters of panobinoast with and without docetaxel.

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

Panobinostat iv formulation (25 mg/5 mL); the initial cohort of patients was dosed with iv panobinostat 10 mg/m^2 (starting dose), administered on Day 1 and 8 in combination with iv docetaxel 75 mg/m^2 on Day 1 and daily oral prednisone 5 mg twice daily. The treatment was repeated every 21 days. The dose of panobinostat was subsequently increased to 15 mg/m^2 and 20 mg/m^2 as tolerated. Batch numbers: Y088 0607; Y195 1107; Y063 0408; U001 0209; Y125 0709.

Docetaxel (Taxotere®) was administered at a dose of 75 mg/m^2 as a 1 hour infusion given every 21 days.

Statistical Methods

The data were analyzed by the Sponsor. All analyses, with the exception of the Bayesian Logistic Regression Model (BLRM), were performed using SAS® Version 9.2. BLRM was performed on SPLUS, Version 8.1. The data from participating centers were combined and all patients were analyzed in one treatment group by different dosing levels. All listings and tables were presented by the single treatment at escalating panobinostat dose levels of 10, 15, 20 mg/m^2 and all patients combined.

The preliminary assessment of the study treatment efficacy was based on the best overall tumor response as per investigator reported tumor assessments, PSA changes from baseline in all 43 patients (Full anaylsis set) as well as on PFS and OS analysis in 25 patients at the MTD. For the PFS analysis, disease progression was taken as a composite endpoint of tumor and/or PSA progression whichever happened first.

The primary variable was the probability of DLT determined in Cycle 1 using the MTD evaluable population during the dose-escalation phase. Determination of the MTD was based on the estimated probability of DLT from the BLRM, application of the overdose control criteria, and all other available clinical safety and laboratory data during dose escalation.

A DLT was defined as an AE or abnormal laboratory value assessed as suspected to be related to study treatment and either occurred within 21 days following Day 1 dosing of panobinostat with docetaxel and prednisone or that delayed the start of the next treatment cycle by > 7 days. Toxicity severity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 3.0. An adaptive BLRM and dose-escalation criteria according to published papers were used to guide dose escalation.

After the patients in each cohort had completed at least 1 treatment cycle, the prior distribution was updated with the accumulated DLT data from Cycle 1. Posterior probabilities of the DLT were summarized. Selection of the next dose was based on these probabilities as well as on all other available clinical safety and laboratory data.

A dose-finding assessment 3 months after the last patient completed Cycle 1 was carried out to determine the MTD. The MTD was declared as the recommended dose level that fell within the targeted toxicity range and was agreed upon by the principal investigators and Sponsor clinical team.

Summary statistics were presented for panobinostat plasma concentrations at each scheduled time point by dose level, except Tmax. Along with summary statistics, coefficient of variation (CV, %) for arithmetic mean, and geometric mean were presented. A statistical analysis was performed for area under the curve (AUCinf) and maximum (peak) concentration of drug (Cmax) of panobinostat associated to the MTD group.

Study Population: Inclusion/Exclusion Criteria and Demographics

Diagnosis and main criteria for inclusion

Chemonaive and docetaxel tolerant adult male patients (≥ 18 years old) with progressive HRPC were enrolled into the dose-escalation phase of this study if they had histologically or cytologically confirmed diagnosis of adenocarcinoma of the prostate and evidence of disease progression. During dose expansion at the MTD, patients who had no prior chemotherapy treatment were enrolled.

Exclusion criteria

- Patients with active central nervous system (CNS) disease or brain metastases (Note: patients who had received prior treatment for the CNS disease and were stable without any steroid treatment for at least 2 months were eligible)
- Patients with a history of invasive malignancies other than adequately treated nonmelanoma skin cancer or other solid tumors curatively treated with no evidence of disease for > 5 years
- Prior radiotherapy ≤ 3 weeks prior to study treatment
- Prior radiopharmaceuticals (strontium, samarium)
- Prior biologic therapy ≤ 28 days prior to study treatment
- Prior therapy with a DACi for treatment of cancer
- Patients who required valproic acid for any medical condition during the study or within 5

days prior to first panobinostat treatment

- Impaired cardiac function, including any one of the following:
  - Cardiac – left ventricular ejection fraction (LVEF) < the lower limit of institutional norm as determined by baseline echography (ECHO) or multi-gated acquisition (MUGA)
  - Complete left bundle branch block, obligate use of a cardiac pacemaker, congenital long QT syndrome, history or presence of ventricular tachyarrhythmias, clinically significant resting bradycardia (< 50 beats per minute [bpm]), QT corrected (QTc) with Fredericia's formula (QTcF) > 450 msec on screening ECG, or right bundle branch block plus left anterior hemiblock (bifascicular 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.
  - History of unstable angina pectoris or acute myocardial infarction (MI) within 6 months of study entry
  - New York Heart Association functional classification III-IV
  - Other clinically significant heart disease (e.g. congestive heart failure, cardiomyopathy, cardiac artery disease, uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen)
- Acute or chronic liver or renal disease with impaired hepatic or renal functions
- Peripheral neuropathy according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grade ≥ 2
- Diarrhea ≥ CTCAE grade 2
- Clinically significant third space fluid accumulation
- Symptomatic pleural effusion
- Concomitant use of drugs that have a risk of prolonging the QT interval or causing torsades de pointes (TdP)
- Concomitant use of CYP3A4/5 inhibitors or inducers, where the treatment could not be discontinued or switched to a different medication prior to starting study treatment
- History of allergic reaction attributed to compounds of similar chemical composition as docetaxel/polysorbate 80.

Participant Flow

Patient disposition by initial dose group (FAS)

Disposition Reason	Panobinostat* 10 mg/m^2 N=8 n (%)	15 mg/m^2 N=10 n (%)	20 mg/m^2 N=25 n (%)	All Patients N=43 n (%)
Enrolled[1]	**8 (100.0)**	**10 (100.0)**	**25 (100.0)**	**43 (100.0)**
Treated[2]	**8 (100.0)**	**10 (100.0)**	**25 (100.0)**	**43 (100.0)**
Discontinued treatment	**8 (100.0)**	**10 (100.0)**	**25 (100.0)**	**43 (100.0)**
Primary reason for end of treatment				
Disease progression	5 (62.5)	4 (40.0)	9 (36.0)	18 (41.9)
Adverse event	1 (12.5)	5 (50.0)	8 (32.0)	14 (32.6)
Patient withdrew consent	2 (25.0)	1 (10.0)	8 (32.0)	11 (25.6)
Discontinued study	8 (100.0)	10 (100.0)	25 (100.0)	43 (100.0)
Primary reason for study completion				
Disease progression	6 (75.0)	6 (60.0)	11 (44.0)	23 (53.5)
Patient withdrew consent	2 (25.0)	3 (30.0)	13 (52.0)	18 (41.9)
New cancer therapy	0	1 (10.0)	1 (4.0)	2 (4.7)

FAS = full analysis set.

*study treatment was panobinostat at the planned dose in combination with docetaxel (75 mg/m2) and prednisone (5 mg).

[1] Patients enrolled in the study to receive study treatment

[2] Patients who received at least 1 dose of study drug or docetaxel

Baseline Characteristics

Demographic summary at baseline by initial dose group (FAS)

Demographics variable	Panobinostat* 10 mg/m^2 N=8 n (%)	15 mg/m^2 N=10 n (%)	20 mg/m^2 N=25 n (%)	All Patients N=43 n (%)
Age (Years)				
n	8	10	25	43
Mean (SD)	63.0 (10.72)	66.5 (6.70)	65.2 (6.54)	65.1 (7.38)
Median	62.5	67.0	66.0	66.0
Range	50.0 - 80.0	53.0 - 74.0	54.0 - 76.0	050.0 - 80.0
Age category (years) – n (%)				
<65	5 (62.5)	3 (30.0)	11 (44.0)	19 (44.2)

≥65	3 (37.5)	7 (70.0)	14 (56.0)	24 (55.8)
Race n (%)				
Caucasian	7 (87.5)	8 (80.0)	22 (88.0)	37 (86.0)
Black	1 (12.5)	2 (20.0)	3 (12.0)	6 (14.0)
Body surface area (m^2)				
n	8	10	25	43
Mean (SD)	2.1 (0.23)	2.1 (0.26)	2.1 (0.32)	2.1 (0.28)
Median	2.1	2.1	2.1	2.1
Range	1.8 - 2.5	1.7 - 2.4	1.8 - 3.0	1.7 - 3.0
Source of patient referral – n (%)				
Physician's own practice	4 (50.0)	7 (70.0)	20 (80.0)	31 (72.1)
Physician referral	4 (50.0)	3 (30.0)	5 (20.0)	12 (27.9)

*study treatment was panobinostat at the planned dose in combination with docetaxel (75 mg/m^2) and prednisone (5 mg).

Outcome measures

Primary Outcome Result(s)

The primary outcome was the MTD assessment. An MTD for the study combination was determined to be iv panobinostat 20 mg/m^2 given on Days 1 and 8 plus iv docetaxel 75 mg/m^2 given on Day 1 and a continuous administration oral prednisone 5 mg/day in a 21-day treatment cycle.

Dose limiting toxicities in Cycle 1 by initial dose group (MTD determining population)

	Panobinostat*			
	10 mg/m^2	**15 mg/m^2**	**20 mg/m^2**	**All Patients**
	N=8	**N=10**	**N=25**	**N=43**
	n (%)	**n (%)**	**n (%)**	**n (%)**
No. of patient in MTD-determining population[1]	7 (87.5)	8 (80.0)	6 (66.7)	21 (77.8)
No. of patient with DLT	1 (12.5)	2 (20.0)	1 (11.1)	4 (14.8)
DLT Event:				
Grade 4 Bradycardia	1 (12.5)	0	0	1 (3.7)
Grade 4 Neutropenia	0	2 (20.0)	1 (11.1)	3 (11.1)

*study treatment was panobinostat at the planned dose in combination with docetaxel (75 mg/m^2) and prednisone (5 mg).

[1]. 6 patients excluded as all required safety assessments for DLT evaluation were not performed.

Secondary Outcome Result(s)

Best overall response as per investigator assessment by initial dose group (FAS)

Description	Panobinostat* 10 mg/m^2 N=8 n (%)	15 mg/m^2 N=10 n (%)	20 mg/m^2 N=25 n (%)	All Patients N=43 n (%)
Best overall response				
Complete response (CR)	0	0	0	0
Partial response (PR)	2 (25.0)	1 (10.0)	4 (16.0)	7 (16.3)
Stable disease (SD)	4 (50.0)	8 (80.0)	13 (52.0)	25 (58.14)
Not evaluable / Unknown	0	1 (10.0)	6 (24.0)	7 (16.28)

*study treatment was panobinostat at the planned dose in combination with docetaxel (75 mg/m^2) and prednisone (5 mg).

Co-administration of docetaxel had marginal impact on panobinostat exposure, suggesting no or minimal DDI potential at the dose administered.

Summary statistics of panobinostat PK parameters by initial dose group (PK population)

PK parameter (unit)	Panobinostat* 10 mg/m^2 N=8	15 mg/m^2 N=10	20 mg/m^2 N=25
Day 1 (panobinostat + docetaxel)			
AUC (0-inf) (ng.h/mL)	210.4 (28.2)	447.7 (26.4)	573.9 (30.8)
Cmax (ng/mL)	87.1 (130.7)	306.8 (63.1)	324.6 (67.2)
Tmax (h)	0.5 [0.5;0.7]	0.5 [0.3;0.7]	0.5 [0.4;2.1]
T1/2 (h)	21.5 (16.7)	20.6 (30.9)	20.5 (36.2)
CL (mL/h)	96300 (37.4)	67900 (28.7)	71800 (36.1)
Vz (mL)	2988000 (48.2)	2021000 (38.8)	2120000 (54.4)
Day 8 (panobinostat alone)			
AUC (0-inf) (ng.h/mL)	234.9 (29.7)	401.5 (19.2)	481.3 (42.7)
Cmax (ng/mL)	127.8 (116.0)	271.0 (55.1)	276.2 (96.9)
Tmax (h)	0.5 [0.5;0.6]	0.5 [0.4;0.7]	0.5 [0.4;1.1]
T ½ (h)	19.2 (25.9)	21.2 (7.9)	22.4 (14.7)
CL (mL/h)	85800 (37.2)	74400 (22.0)	84600 (37.1)
Vz (mL)	2376000 (47.6)	2270000 (18.8)	2740000 (39.1)

AUC = area under the curve; CL = clearance; Cmax = maximum concentration of drug; CV = coefficient of variance; PK = pharmacokinetic; T1/2 = terminal elimination half-life; Tmax = time to peak concentration; Vz = volume of distribution.

*study treatment was panobinostat at the planned dose in combination with docetaxel (75 mg/m2) and prednisone (5 mg).

Values are median (range) for Tmax, and geometric mean (CV% geometric mean) for all other parameters.

Safety Results

Adverse Events by System Organ Class (Safety Population)

Adverse events, regardless of study drug relationship, by primary system organ class (≥ 60%, any grade) and initial dose group

	Panobinostat*							
	10mg/m^2 N=8		15mg/m^2 N=10		20mg/m^2 N=25		All patients N=43	
Primary system organ class	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)	Any grade n (%)	Grade 3/4 n (%)
Any system organ class - Total	8 (100.0)	8 (100.0)	9 (90.0)	9 (90.0)	25 (100.0)	24 (96.0)	42 (97.7)	41 (95.3)
Blood and lymphatic system disorders	8 (100.0)	8 (100.0)	9 (90.00)	8 (80.0)	22 (88.0)	20 (80.0)	39 (90.7)	36 (83.7)
General and administration site disorders	6 (75.0)	0 (0.0)	8 (80.0)	0 (0.0)	23 (92.0)	6 (24.0)	37 (86.0)	6 (14.0)
Gastrointestinal disorders	5 (62.5)	0 (0.0)	8 (80.0)	1 (10.0)	19 (76.0)	1 (4.0)	32 (74.4)	2 (4.7)
Nervous system disorders	4 (50.0)	2 (25.0)	6 (60.0)	2 (20.0)	20 (80.0)	1 (4.0)	30 (69.8)	5 (11.6)
Metabolism and nutrition disorders	4 (50.0)	0 (0.0)	7 (70.0)	1 (10.0)	18 (72.0)	6 (24.0)	29 (67.4)	7 (16.3)
Investigations	2 (25.0)	1 (12.5)	6 (60.0)	4 (40.0)	19 (76.0)	11 (44.0)	27 (62.8)	16 (37.2)

- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.

- A patient with multiple adverse events within a primary system organ class is counted only once in the total row.

- Includes all adverse events since first study drug and up to 28 days after last dose.

*study treatment was panobinostat at the planned dose in combination with docetaxel (75 mg/m^2) and prednisone (5 mg).

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

Adverse events suspected to be related to study treatment occurring in at least 10% of the patients by preferred term and initial dose group (Safety population)

	Panobinostat*						All patients	
	10 mg/m^2 N=8		15 mg/m^2 N=10		20 mg/m^2 N=25			
	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 (%)**
Any preferred term	**8 (100.0)**	**8 (100.0)**	**9 (90.0)**	**9 (90.0)**	**25 (100.0)**	**24 (96.0)**	**42 (97.7)**	**41 (95.3)**
Fatigue	6 (75.0)	0	7 (70.00)	0	19 (76.00)	6 (24.0)	32 (74.4)	6 (14.0)
Neutropenia	6 (75.0)	6 (75.0)	6 (60.0)	6 (60.0)	15 (60.0)	15 (60.0)	27 (62.8)	27 (62.8)
Dyspnoea	2 (25.0)	0	4 (40.0)	0	13 (52.0)	1 (4.0)	19 (44.2)	1 (2.3)
Thrombocytopenia	3 (37.5)	0	1 (10.0)	0	15 (60.0)	8 (32.0)	19 (44.2)	8 (18.6)
Diarrhoea	2 (25.0)	0	2 (20.0)	0	12 (48.0)	0	16 (37.2)	0
Nausea	1 (12.5)	0	5 (50.0)	0	10 (40.0)	0	16 (37.2)	0
Hyperglycemia	2 (25.0)	0	1 (10.0)	0	11 (44.0)	5 (20.0)	14 (32.6)	5 (11.6)
Odema peripheral	1 (12.5)	0	2 (20.0)	0	11 (44.0)	0	14 (32.6)	0
Anaemia	1 (12.5)	0	2 (20.0)	1 (10.0)	10 (40.0)	2 (8.0)	13 (30.2)	3 (7.0)
Leukopenia	5 (62.5)	1 (12.5)	2 (20.0)	2 (20.0)	6 (24.0)	6 (24.0)	13 (30.2)	9 (20.9)

AEs = adverse events; PT = preferred term.

*study treatment was panobinostat at the planned dose in combination with docetaxel (75 mg/m2) and prednisone (5 mg).

AEs are sorted by PT by descending order of frequency in the All Patients 'All grades' column.

Serious Adverse Events and Deaths

Deaths, other or related serious or clinically significant adverse events or discontinuations by initial dose group (Safety population)

	Panobinostat*			All patients
	10 mg/m^2	15 mg/m^2	20 mg/m^2	
	N=8	N=10	N=25	
	n (%)	n (%)	n (%)	n (%)
Patients with any AE[1]	**8 (100.0)**	**9 (90.0)**	**25 (100.0)**	**42 (97.7)**
Serious or other significant event				
All deaths[2]	6 (75.0)	8 (80.0)	15 (60.0)	29 (67.4)
Deaths (on treatment)[3]	0	0	1 (4.0)	1 (2.3)
All SAEs	4 (50.0)	8 (80.0)	14 (56.0)	26 (60.5)
Study drug-related SAEs	3 (37.5)	6 (60.0)	11 (44.0)	20 (46.5)
AEs leading to discontinuation	1 (12.5)	5 (50.0)	7 (28.0)	13 (30.2)

AE = adverse event; CRF = case report form; SAE = serious adverse event.

*study treatment was panobinostat at the planned dose in combination with docetaxel (75 mg/m2) and prednisone (5 mg).

[1] Adverse events (including SAEs and AEs leading to discontinuation) that occurred on treatment and up to 28 days after the last dose of study drug.

[2] Includes all deaths as reported in Survival and study completion CRF page.

[3] Deaths that occurred on treatment (the only death was due to PD).

Other Relevant Findings

- •Hematology: Most of the reported abnormalities were of grade 3 or 4 (WBC [79.1%], neutrophils [87.5%], and lymphocytes [62.5%]. Their incidence did not appear to be dose-dependent. The incidence of grade 3 or 4 platelet count (25.6%) appeared to increase by increasing panobinostat dose levels. Grade 3 or 4 low hemoglobin was infrequently reported (18.6%). Coagulation parameters were not affected in any significant manner.
- The most frequently reported clinical chemistry abnormalities were hyperglycemia (68.3%), hypoalbuminemia (64.3%), hypocalcemia (51.2%) and hypophosphatemia (47.6%).
- No clinically relevant pattern was evident in vital signs changes with resolution of observed changes by the end of study.
- A post-baseline QTcF increase of > 30 msec was noted in 51.2% of the patients with only

2 patients having an increase in QTcF of > 60 msec. A maximum post-baseline QTcF value > 500 msec was observed in one patient. Other common ECG abnormalities included T-waves morphologic changes and depressed ST-segment. There were no cases of Torsade de Points.
Date of Clinical Trial Report 07-Dec-2012
Date Inclusion on Novartis Clinical Trial Results Database 16-Jan-2013
Date of Latest Update