Sponsor

Novartis

Generic Drug Name

Panobinostat

Therapeutic Area of Trial

Breast cancer

Approved Indication

Investigational

Study Number

CLBH589C2114

Title

A phase Ib, open-label, two arm study of i.v. and oral panobinostat (LBH589) in combination with i.v. trastuzumab (Herceptin®) and i.v. paclitaxel as treatment for adult female patients with HER2 overexpressing metastatic breast cancer (MBC)

Phase of Development

Phase 1b

Study Start/End Dates

15 Dec 2008 to 03 Aug 2010

Following review of available data on 29 Sep 2009 from this study, and a similar study evaluating panobinostat (i.v. and oral) in combination with trastuzumab in patients with HER2+ MBC (study CLBH589C2204), further enrollment was stopped by the sponsor as of 12 Oct 2009 due to insufficient evidence of clinical benefit.

Study Design/Methodology

This was a phase 1b open label, multi-centre, two-arm, global study of i.v. panobinostat and oral panobinostat given in combination with weekly paclitaxel and weekly trastuzumab in women with HER2-positive MBC.

A minimum of 3 patients were enrolled into a cohort, unless further enrollment was prematurely stopped. In each successive cohort, patients received an increased dose of panobinostat with standard doses of trastuzumab and paclitaxel until the MTD was reached.

The starting dose for i.v. panobinostat (Arm I) was 10 mg/m^2 given once a week (e.g. D1 and D8) for two weeks on treatment with one week off treatment as part of a 21 day treatment cycle.

The starting dose for oral panobinostat (Arm II) was 10 mg given three times every week (e.g. Day 1, D3, and D5 weekly) given as part of a 21 day treatment cycle.

In each arm, at least 9 patients were to be treated with panobinostat at a given dose before it could be declared the MTD for panobinostat given with trastuzumab and paclitaxel. Once the MTD was determined, a dose-expansion phase was to be initiated to enroll additional patients for safety and tolerability evaluation of the study treatment combination. In addition to the 9 patients needed to determine MTD, the dose expansion phase was planned to include 11 patients more at the MTD level, leading to a total exposure of 20 patients at the MTD level for each treatment arm.

Centres

7 centers in 5 countries: Australia (1 site), Belgium (2 sites), Italy (2 sites), Netherlands (1 site), and US (1 site)

Publication

None

Objectives

Primary objective(s)

- Arm I: to determine the maximum-tolerated dose (MTD) based on dose-limiting toxicities (DLT) of i.v. panobinostat given weekly for two weeks on treatment, one week off treatment (e.g. D1, D8 as part of a 21 day cycle) when given in combination with weekly paclitaxel and weekly trastuzumab in patients with HER2 positive MBC.
- Arm II: to determine the maximum-tolerated dose (MTD) based on dose-limiting toxicities (DLT) of oral panobinostat given three times a week (e.g. on days 1, 3 and 5 every week as part of a 21 day cycle) when given in combination with weekly paclitaxel and weekly trastuzumab in patients with HER2 positive MBC.

Secondary objective(s)

- To characterize the safety and tolerability of i.v. and oral panobinostat when given in combination with paclitaxel and trastuzumab.
- To evaluate the effect on QTc interval in patients receiving i.v. and oral panobinostat when given in combination with paclitaxel and trastuzumab.
- To characterize the pharmacokinetics of panobinostat following i.v. and oral administration of panobinostat in combination with paclitaxel and trastuzumab in patients enrolled at dose expansion phase.
- To describe the pharmacokinetics of paclitaxel alone and in combination with panobinostat and trastuzumab in patients enrolled at dose expansion phase.
- To explore preliminary antitumor activity of panobinostat when given intravenously (Arm I) and orally (Arm II) in combination with weekly paclitaxel and weekly trastuzumab.

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

For Arm I, panobinostat at starting dose of 10 mg/m^2 i.v. on a Day 1 and Day 8 schedule (2 weeks on treatment, 1 week off) as part of a 21 day cycle.

For Arm II, panobinostat administered by oral route at starting dose of 10 mg three times a week for 3 weeks as part of a 21 day cycle.

For both treatment arms, paclitaxel (80 mg/m^2 , i.v. infusion) and trastuzumab (Loading dose: 4mg/kg infusion given over 90 min, Maintenance dose: 2mg/kg infusion given for 30 min) were administered weekly on a 21-day cycle on Days 1, 8, and 15.

In each successive cohort, patients received an increased dose of panobinostat with standard doses of trastuzumab and paclitaxel until the MTD was reached.

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

None

Criteria for Evaluation

Primary variables

Dose-limiting toxicity (DLT) was the primary variable for the MTD assessment.

Secondary variables

Safety and tolerability: The safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs), with their severity and relationship to study drug, and pregnancies. Regular monitoring of vital signs, physical examination, ECOG PS, cardiac function (LVEF and ECGs), hematology, coagulation parameters, biochemistry, thyroid function test, and urinalysis were performed by local assessment. Following local assessment, all ECGs were centrally reviewed by an independent reviewer.

No PK-analyses were conducted since the expansion phase with PK sampling was not initiated.

Efficacy: Antitumor activity was evaluated using overall objective tumor response based on the RECIST criteria using the Novartis Oncology RECIST Guideline.

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

The patients had baseline evaluations performed ≤ 28 days prior to study treatment start (cycle 1 Day 1). The results for each patient were reviewed by the Principal Investigator or his/her designee prior to study enrollment to ensure that all inclusion and exclusion criteria were satisfied.

Inclusion criteria

- Histologically or cytologically confirmed HER2+ breast cancer with radiological evidence of metastatic disease progressing at study entry
- Female patients ≥ 18 years old
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of ≤ 1
- Non-measurable or measurable disease according to Response Evaluation Criteria In Solid Tumors (RECIST)
- Prior treatment for brain metastases was allowed but patients were to be neurologically stable and off corticosteroids and not receiving concurrent radiotherapy for brain metastases
- Prior treatment with trastuzumab and/or lapatinib was permitted. Trastuzumab was to be given ≤ 4 weeks prior to study treatment start. Last lapatinib dose was to have been administered ≥ 2 weeks prior to the start of study treatment
- If patient has received prior treatment with anthracylines, this was to be completed ≥ 24

weeks before the start of study treatment

- Patient must have received at least one prior treatment regimen containing a taxane and up to 2 prior regimens for metastatic disease
- Concurrent bisphosphonates were permitted if initiated prior to study entry (at least 4 weeks before study entry)
- Patients were to meet the following laboratory criteria
- Hematology
  - Neutrophil count of >1500/mm^3
  - Platelet count of > 100,000/mm^3
  - Hemoglobin ≥ 9 g/dL
- Biochemistry
  - AST/SGOT and ALT/SGPT ≤ 2.5 x upper limit of normal (ULIN) or ≤ 5.0 x ULIN in case of liver metastases
  - Serum bilirubin ≤ 1.5 x ULIN
  - Serum creatinine ≤ 1.5 x ULIN or 24-hour creatinine clearance ≥ 50 mL/min
  - Total serum calcium (corrected for serum albumin) or ionized calcium ≥ LLIN and ≤ ULIN
  - Serum potassium, sodium, magnesium, phosphatase ≥ LLIN and ≤ ULIN
  - Serum albumin ≥ LLIN or 3g/dL
- Patients with elevated alkaline phosphatase due to bone metastasis could be enrolled
- Patient who are clinically euthyroid (patients could be on thyroid hormone replacement)
- Potassium, calcium, and magnesium supplements could be given to correct values that are < LLIN, but were to be documented as corrected prior to patients enrolling on the study
- Women of childbearing potential were to have a negative serum pregnancy test within 7 days of the first administration of study treatment and were to be willing to use adequate methods of contraception during the study and for 3 months after last study drug administration.

Exclusion criteria

- Prior histone deacetylase, deacetylase, HSP90 inhibitors or valproic acid administered for the treatment of cancer
- Need for valproic acid during the study or within 5 days prior to first panobinostat treatment
- History of hypersensitivity reaction to paclitaxel or other drugs formulated with polysorbate 80 (Tween 80), polyethoxylated castor oil
- Known allergy or severe reactions to paclitaxel or its constituents
- Known allergy or severe reactions to trastuzumab or its constituents
- Prior chemotherapy within the last 3 weeks (exceptions: ≥ 6 weeks for nitrosoureas or mitomycin, ≥ 2 weeks for capecitabine or oral cyclophosphamide) before the start of study treatment
- Prior treatment with investigational agents within the last 4 weeks before the start of study treatment

- Surgery within the last 2 weeks prior to starting study treatment or not having recovered from such therapy
- Presence of persistent ≥ Grade 2 neuropathy or history of Grade 3/4 neuropathy of any etiology
- Presence of unresolved diarrhea ≥ Grade 1according to common terminology criteria for adverse events (CTCAE).
- Impaired cardiac function, including any one of the following:
  - Left ventricular ejection fraction (LVEF) < 50%
  - 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 [bpm]) or QTc > 450 ms on screening ECG or right bundle branch block and left anterior hemi block (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
  - Previous history angina pectoris or acute MI within 6 months
  - Congestive heart failure (New York Heart Association functional classification 3-4)
  - Other clinically significant heart disease (e.g. cardiomyopathy, cardiac artery disease, uncontrolled hypertension or history of poor compliance with an antihypertensive regimen)
- Concomitant use of drugs with a risk of causing torsades de pointes when such treatment could not be discontinued or switched to a different medication prior to starting study drug
- Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes mellitus, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease including dyspnoea at rest from any cause) that could cause unacceptable safety risks or compromise compliance with the protocol
- Known history of HIV seropositivity (baseline HIV testing was not required)
- Active bleeding diathesis or ongoing treatment with therapeutic doses of sodium warfarin or any other anti-vitamin K drugs (mini-dose of Coumadin®, e.g. 1 mg/day, or other agents given to maintain intravenous line patency and unfractionated or low molecular weight heparin therapy was permitted).
- Requirement of diuretics or draining procedures to manage or drain third space fluid accumulation
- Bone marrow support, stem cell support at study entry
- Pregnant or breast-feeding
- History of non-compliance with medical treatments or inability to grant a reliable written informed consent

Number of Subjects

Patient disposition by arm and assigned dose level (FAS)

Disposition reason	I.V. 10 mg/m² N=3 n (%)	I.V. 15 mg/m² N=4 n (%)	I.V. All N=7 n (%)	Oral 10 mg N=6 n (%)
Enrolled[1]	3 (100)	4 (100)	7 (100)	6 (100)
Discontinued treatment	3 (100)	4 (100)	7 (100)	6 (100)
Discontinued study	3 (100)	4 (100)	7 (100)	6 (100)
Primary reason for end of treatment				
Adverse Event(s)	0	1 (25.0)	1 (14.3)	3 (50.0)
Disease progression	3 (100)	3 (75.0)	6 (85.7)	3 (50.0)
Primary reason for study evaluation completion				
Subject withdrew consent	0	1 (25.0)	1 (14.3)	1 (16.7)
Administrative problems	0	0	0	1 (16.7)
Disease progression	3 (100)	3 (75.0)	6 (85.7)	4 (66.7)
[1] Treated with at least one dose of study drug				

Demographic and Background Characteristics

Demographic summary by arm and assigned dose level (FAS)

Demographic variable	I.V. 10 mg/m² N=3	I.V. 15 mg/m² N=4	I.V. All N=7	Oral 10 mg N=6
Baseline age (years)				
N	3	4	7	6
Median	52.0	48.5	51.0	62.0
Min – Max	40-68	41-58	40-68	47-71
Baseline age category (years) - n (%)				
<65	2 (66.7)	4 (100)	6 (85.7)	3 (50.0)
>=65	1 (33.3)	0	1 (14.3)	3 (50.0)
Race - n (%)				
Caucasian	3 (100)	3 (75.0)	6 (85.7)	6 (100)
Black	0	1 (25.0)	1 (14.3)	0
Baseline BSA (m²)				
N	3	4	7	6
Median	1.700	1.745	1.700	1.660
Min – Max	1.68-2.07	1.66-2.30	1.66-2.30	1.58-1.91

Primary Objective Result(s)

Due to early cessation of the study, the MTD was not established in any treatment arm.

Dose limiting toxicities in cycle 1 by arm and assigned dose level (Safety set)

DLT information	I.V. 10 mg/m² N=3 n (%)	I.V. 15 mg/m² N=4 n (%)	I.V. All N=7 n (%)	Oral 10 mg N=6 n (%)
No. Patients with DLT	0 (0.0)	1 (25.0)	1 (14.3)	1 (16.7)
DLT event				
Abdominal pain	0 (0.0)	1 (25.0)	1 (14.3)	0 (0.0)
Diarrhea	0 (0.0)	1 (25.0)	1 (14.3)	1 (16.7)
Vomiting	0 (0.0)	1 (25.0)	1 (14.3)	0 (0.0)
Worsening nausea	0 (0.0)	1 (25.0)	1 (14.3)	0 (0.0)

Secondary Objective Result(s)

Number and percentage of patients with notable QT interval values by arm and assigned dose level (Safety set)

	I.V. 10 mg/m² N=3		I.V. 15 mg/m² N=4		I.V. All N=7		Oral 10 mg N=6	
	Total	n (%)	Total	n (%)	Total	n (%)	Total	n (%)
Maximum QTcF value								
>=450 ms and < 480 ms	3	1 (33.3)	4	0	7	1 (14.3)	6	0
>=480 ms and < 500 ms	3	0	4	0	7	0	6	0
>=500 ms and < 515 ms	3	0	4	0	7	0	6	0
>=515 ms	3	0	4	0	7	0	6	0
Maximum QTcF increase from baseline								
30-60 ms	3	0	4	0	7	0	6	2 (33.3)
>60 ms	3	1 (33.3)	4	0	7	1 (14.3)	6	0
A notable QT interval was defined as an increase of >60 ms in QTcF or an absolute QTcF of >500 ms								
For the maximum QTcF value, total is the number of patients with a measurement at baseline.								
For the maximum QTcF increase from baseline, total is the number of patients with a measurement at baseline and post-baseline.								

Overall antitumor response rate by Investigator assessment by arm and assigned dose level (FAS patients)

Best overall response according to RECIST	I.V. 10 mg/m² N=3	I.V. 15 mg/m² N=4	I.V. All N=7	Oral 10 mg N=6
Complete response (CR)	0	0	0	1 (16.7)
Partial response (PR)	1 (33.3)	0	1 (14.3)	0
Stable disease (SD)	2 (66.7)	2 (50.0)	4 (57.1)	4 (66.7)
Progressive disease (PD)	0	1 (25.0)	1 (14.3)	0
Unknown	0	1 (25.0)	1 (14.3)	1 (16.7)

Best overall response is calculated according to RECIST guidelines using investigator's overall lesion response. Following data lock, a patient's (treated with 15 mg/m^2 i.v. panobinostat) overall response was confirmed to be a PR from SD by the Investigator (data not shown in the table above).

Safety Results

Adverse Events by System Organ Class

From TABLE 14.3.1-1.1

Adverse events, regardless of study drug relationship, by primary system organ class, maximum grade and by arm and assigned dose level
Population: Safety set (SAF)

Any primary system organ class	I.V. 10 mg/m²		I.V. 15 mg/m²		I.V. All		Oral 10 mg	
	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4	All grades	Grade 3/4
Total	3(100)	3 (100)	4 (100)	4 (100)	7 (100)	7 (100)	6 (100)	6 (100)
Blood and lymphatic system disorders	3(100)	2(66.7)	4 (100)	2(50.0)	7 (100)	4(57.1)	4(66.7)	3(50.0)
Cardiac disorders	1(33.3)	0	2(50.0)	0	3(42.9)	0	0	0
Ear and labyrinth disorders	0	0	0	0	0	0	2(33.3)	0
Endocrine disorders	0	0	0	0	0	0	1(16.7)	0
Eye disorders	1(33.3)	0	0	0	1(14.3)	0	2(33.3)	0
Gastrointestinal disorders	3(100)	0	4 (100)	1(25.0)	7 (100)	1(14.3)	6 (100)	1(16.7)
General disorders and administration site conditions	3(100)	1(33.3)	3(75.0)	0	6(85.7)	1(14.3)	6 (100)	2(33.3)
Hepatobiliary disorders	0	0	0	0	0	0	1(16.7)	0
Infections and infestations	3(100)	1(33.3)	3(75.0)	0	6(85.7)	1(14.3)	5(83.3)	2(33.3)
Injury, poisoning and procedural complications	1(33.3)	0	0	0	1(14.3)	0	0	0
Investigations	2(66.7)	1(33.3)	1(25.0)	0	3(42.9)	1(14.3)	1(16.7)	1(16.7)
Metabolism and nutrition disorders	2(66.7)	0	2(50.0)	0	4(57.1)	0	1(16.7)	0
Musculoskeletal and connective tissue disorders	2(66.7)	0	2(50.0)	0	4(57.1)	0	3(50.0)	1(16.7)

Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	0	1(16.7)	1(16.7)
Nervous system disorders	3(100)	0	2(50.0)	1(25.0)	5(71.4)	1(14.3)	6 (100)	0
Psychiatric disorders	2(66.7)	0	0	0	2(28.6)	0	1(16.7)	0
Renal and urinary disorders	0	0	0	0	0	0	1(16.7)	0
Respiratory, thoracic and mediastinal disorders	3(100)	0	1(25.0)	0	4(57.1)	0	4(66.7)	0
Skin and subcutaneous tissue disorders	3(100)	0	0	0	3(42.9)	0	5(83.3)	0
Vascular disorders	1(33.3)	0	0	0	1(14.3)	0	2(33.3)	0

- 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.
- All adverse events on treatment and up to 28 days after last dose are included.

Adverse events experienced by more than one patient regardless of study drug relationship, by preferred term, maximum grade, arm and assigned dose level (Safety set)

	I.V. 10 mg/m² N=3		**I.V. 15 mg/m² N=4**		**I.V. All N=7**		**Oral 10 mg N=6**	
Preferred term	**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 preferred term	3 (100)	3 (100)	4 (100)	4 (100)	7 (100)	7 (100)	6 (100)	6 (100)
Neutropenia	3 (100)	2 (66.7)	3 (75.0)	2 (50.0)	6 (85.7)	4 (57.1)	4 (66.7)	3 (50.0)
Diarrhoea	2 (66.7)	0	3 (75.0)	1 (25.0)	5 (71.4)	1 (14.3)	5 (83.3)	1 (16.7)
Nausea	1 (33.3)	0	4 (100)	1 (25.0)	5 (71.4)	1 (14.3)	5 (83.3)	0
Abdominal pain	1 (33.3)	0	3 (75.0)	1 (25.0)	4 (57.1)	1 (14.3)	1 (16.7)	0

Alopecia	3 (100)	0	0	0	3 (42.9)	0	4 (66.7)	0
Constipation	1 (33.3)	0	2 (50.0)	0	3 (42.9)	0	2 (33.3)	0
Epistaxis	2 (66.7)	0	1 (25.0)	0	3 (42.9)	0	2 (33.3)	0
Mouth ulceration	2 (66.7)	0	1 (25.0)	0	3 (42.9)	0	2 (33.3)	0
Asthenia	1 (33.3)	0	2 (50.0)	0	3 (42.9)	0	1 (16.7)	1 (16.7)
Influenza	1 (33.3)	0	2 (50.0)	0	3 (42.9)	0	0	0
Leukopenia	2 (66.7)	1 (33.3)	1 (25.0)	0	3 (42.9)	1 (14.3)	0	0
Cough	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	3 (50.0)	0
Back pain	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	2 (33.3)	0
Dysgeusia	2 (66.7)	0	0	0	2 (28.6)	0	2 (33.3)	0
Dyspepsia	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	2 (33.3)	0
Paraesthesia	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	2 (33.3)	0
Pyrexia	0	0	2 (50.0)	0	2 (28.6)	0	2 (33.3)	0
Vomiting	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	2 (33.3)	0
Abdominal discomfort	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	1 (16.7)	0
Anaemia	0	0	2 (50.0)	0	2 (28.6)	0	1 (16.7)	0
Decreased appetite	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	1 (16.7)	0
Muscle spasms	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	1 (16.7)	0
Thrombocytopenia	0	0	2 (50.0)	0	2 (28.6)	0	1 (16.7)	1 (16.7)
Vaginal infection	2 (66.7)	0	0	0	2 (28.6)	0	1 (16.7)	0
Gastrointestinal motility								
Disorder	0	0	2 (50.0)	0	2 (28.6)	0	0	0
Musculoskeletal pain	0	0	2 (50.0)	0	2 (28.6)	0	0	0
Palpitations	1 (33.3)	0	1 (25.0)	0	2 (28.6)	0	0	0
Abdominal pain upper	1 (33.3)	0	0	0	1 (14.3)	0	3 (50.0)	0
Fatigue	1 (33.3)	0	0	0	1 (14.3)	0	2 (33.3)	0
Stomatitis	1 (33.3)	0	0	0	1 (14.3)	0	2 (33.3)	0
Arthralgia	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Cystitis	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Dry mouth	0	0	1 (25.0)	0	1 (14.3)	0	1 (16.7)	0
Dyspnoea exertional	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Ear infection	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Eye oedema	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Febrile neutropenia	0	0	1 (25.0)	1 (25.0)	1 (14.3)	1 (14.3)	1 (16.7)	0
Gingivitis	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Headache	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Insomnia	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Lymphoedema	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Muscular weakness	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Nail discolouration	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Nasopharyngitis	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Peripheral sensory neuropathy	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0

Pharyngitis	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Skin infection	1 (33.3)	0	0	0	1 (14.3)	0	1 (16.7)	0
Urinary tract infection	0	0	1 (25.0)	0	1 (14.3)	0	1 (16.7)	0
Oedema peripheral	0	0	0	0	0	0	3 (50.0)	0
Bronchitis	0	0	0	0	0	0	2 (33.3)	0
Infection	0	0	0	0	0	0	2 (33.3)	0
Myalgia	0	0	0	0	0	0	2 (33.3)	1 (16.7)
Nail disorder	0	0	0	0	0	0	2 (33.3)	0
Neuropathy peripheral	0	0	0	0	0	0	2 (33.3)	0
Vertigo	0	0	0	0	0	0	2 (33.3)	0
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.								
- All adverse events on treatment and up to 28 days after last dose are included.								

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

The most frequent adverse events included neutropenia, anaemia, thrombocytopenia, diarrhoea, nausea, abdominal discomfort, abdominal pain, dyspepsia, mouth ulceration, paraesthesia, pyrexia, asthenia, alopecia, and dysgeusia.

Serious Adverse Events and Deaths

Summary of adverse event categories in the study by arm and assigned dose level (Safety set)

Adverse event information	I.V. 10 mg/m² N=3 n (%)	I.V. 15 mg/m² N=4 n (%)	I.V. All N=7 n (%)	Oral 10 mg N=6 n (%)
Patient with AE(s) [1]	3 (100)	4 (100)	7 (100)	6 (100)
Deaths [2] (on treatment)	0	0	0	0
Grade 3-4 AEs	3 (100)	4 (100)	7 (100)	6 (100)
All serious AE	1 (33.3)	1 (25.0)	2 (28.6)	4 (66.7)
Study-drug-related SAEs	0	1 (25.0)	1 (14.3)	2 (33.3)
AE leading to discontinuation [3]	0	1 (25.0)	1 (14.3)	4 (66.7)
[1]. Adverse events occurring up to than 28 days after the discontinuation of study treatment are not summarized.				
[2]. Deaths occurring more than 28 days after the discontinuation of study treatment are not summarized.				
[3]. As reported in AE CRF page (including one patient discontinued from paclitaxel due to paraesthesia and later discontinued from panobinostat due to disease progression).				

Serious adverse events, by preferred term, maximum grade, arm and assigned dose level (Safety set)

	I.V. 10 mg/m² N=3		I.V. 15 mg/m² N=4		I.V. All N=7		Oral 10 mg N=6	
Preferred term	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 preferred term	1 (33.3)	1 (33.3)	1 (25.0)	1 (25.0)	2 (28.6)	2 (28.6)	4 (66.7)	4 (66.7)
Abdominal pain	0	0	1 (25.0)	1 (25.0)	1 (14.3)	1 (14.3)	1 (16.7)	0
Diarrhoea	0	0	1 (25.0)	1 (25.0)	1 (14.3)	1 (14.3)	1 (16.7)	1 (16.7)
Nausea	0	0	1 (25.0)	1 (25.0)	1 (14.3)	1 (14.3)	1 (16.7)	0
Vomiting	0	0	1 (25.0)	0	1 (14.3)	0	1 (16.7)	0
Catheter sepsis	1 (33.3)	1 (33.3)	0	0	1 (14.3)	1 (14.3)	0	0
Asthenia	0	0	0	0	0	0	1 (16.7)	0
ECOG PS worsened	0	0	0	0	0	0	1 (16.7)	1 (16.7)

General physical health Deterioration	0	0	0	0	0	0	1 (16.7)	1 (16.7)
Labyrinthitis	0	0	0	0	0	0	1 (16.7)	1 (16.7)
Metastatic pain	0	0	0	0	0	0	1 (16.7)	1 (16.7)
Pneumonia	0	0	0	0	0	0	1 (16.7)	1 (16.7)
- A patient with multiple occurrences of an AE under one treatment is counted only once in the AE category for that treatment.								
- All adverse events on treatment and up to 28 days after last dose are included.								

Other Relevant Findings

None

Date of Clinical Trial Report

10 Jun 2011

Date Inclusion on Novartis Clinical Trial Results Database

28 Jun 2011

Date of Latest Update