Sponsor Novartis
Generic Drug Name Panobinostat
Therapeutic Area of Trial HER2+Metastatic Breast Cancer
Approved Indication Investigational
Protocol Number CLBH589C2204
Title A phase Ib/IIa, trial of LBH589 in combination with trastuzumab in adult female patients with HER2 positive metastatic breast cancer whose disease has progressed during or following therapy with trastuzumab
Phase of Development Phase Ib/IIa
Study Start/End Dates 10-Apr-2008 to 02-May-2011 Enrollment was stopped prematurely by the sponsor as of 12-Oct-2009 due to insufficient efficacy.
Study Design/Methodology Open label, multicenter, randomized, two-arm, international study investigating i.v. and oral administration of panobinostat in combination with trastuzumab in women with HER2 positive MBC progressing on or after treatment with a trastuzumab containing regimen. The study design included a dose escalation phase and a dose expansion phase at the MTD level.
Centres 29 centers from 6 enrolling countries: Canada (3), France (4), Germany (2), Italy (3), United Kingdom (3), and United States (14).

Publication

None

Outcome measures

Primary outcome measure(s)

Dose escalation phase: Dose-limiting toxicity (DLT) for the MTD assessment.

Dose expansion phase: Overall response rate (ORR) as per RECIST criteria.

Secondary outcome measure(s)

Efficacy: Dose escalation phase: Preliminary evaluation of anti-tumor activity at the MTDs for both schedules, using best overall response (BOR).

Safety: AEs, SAEs, cardiac safety (central ECGs readings, QTc interval assessment), hematology and biochemistry lab values.

PK profile of i.v. and oral panobinostat in combination with trastuzumab (dose escalation only).

Serum HER2 ECD, circulating tumor cells and apoptosis markers, pre- and post-therapy FDG-PET imaging.

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

i.v.

- Arm I: A starting dose of 10 mg/m^2 over a 30-minute infusion on D1 and D8 of a 21-day cycle combined with standard doses of trastuzumab i.v. weekly.

Oral

- Arm II Cohort 1/Schedule A: A starting dose of 20 mg twice weekly for D1, D4, D8, and D11 of a 21-day cycle combined with standard dose of trastuzumab i.v. weekly.
- Arm II Cohort 2/Schedule B: A starting dose of 15 mg given 3 times daily in D1, 3, 5, 8,10,12,15,17,and 19 of a 21-day cycle combined with standard dose of trastuzumab i.v. weekly.

Statistical Methods

DLT for the MTD assessment was the primary endpoint during the dose escalation phase. Protocol-specified DLTs criteria comprised of AEs or abnormal laboratory values occurring in Cycle 1and assessed as clinically relevant and meeting any of the following criteria:

- considered to be related to the study treatment
- unrelated to disease, PD, inter-current illness, or concomitant medications

Toxicities were assessed using the NCI CTCAE, version 3.0.

Disease-related symptoms were not considered a DLT.

During dose escalation phase, determination of the MTD was based on the estimation of the probability of DLT in cycle 1 and other safety and laboratory data in the MTD analysis set. An adaptive Bayesian logistic regression model and dose escalation criteria were used to guide dose escalation.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

1. Female patients ≥ 18 years old.
2. Patients with an ECOG PS of ≤2.
3. Histologically or cytologically confirmed breast cancer with radiological evidence of metastatic disease.
   - During dose escalation, non-measurable or measurable disease according to RECIST.
   - During dose expansion, measurable disease only was acceptable.
4. History of HER2 + MBC (ICH_3+ staining or FISH (+) or ICH_2+ only if FISH (+). Whenever feasible HER2 status was to be confirmed at metastatic stage of the disease at baseline and post-treatment. HR status (ER/PR) was irrelevant to study population.
5. Prior trastuzumab-containing regimen (in neoadjuvant and/or adjuvant and/or metastatic setting) regardless if trastuzumab was given as monotherapy or in combination with chemotherapy. Any number of prior trastuzumab regimens was acceptable.
6. Radiological evidence of PD while on trastuzumab or within 6 months after last dose of trastuzumab.
7. Radiological evidence of PD on or following most recent therapy within 3 months of study entry.
8. Up to 2 prior chemotherapy regimens for treatment of MBC (including chemotherapy treatment in combination with trastuzumab).

Exclusion Criteria

1. Prior HDAC, DAC, HSP90 inhibitors or valproic acid for the treatment of cancer.
2. Patients who will need valproic acid for any medical condition during the study or within 5

days prior to first panobinostat treatment.

3. Patients who have received prior chemotherapy within the last 4 weeks (6 weeks for nitrosoureas and mitomycin; 2 weeks for capecitabine).
4. Patients who have received prior radiotherapy within the last 4 weeks.
5. Patients who have received prior investigational agents within the last 4 weeks.
6. Patients who have received prior radiotherapy to ≥30% of the bone marrow.
7. Patients with unresolved diarrhea ≥CTCAE grade 1.
8. Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of oral panobinostat.

Participant Flow

Patient disposition by assigned dose level – i.v. arm (FAS)

	10mg/m2 N=7	15mg/m2 N=7	20mg/m2 N=21	All N=35
Treated with at least 1 dose	7(100.0)	7(100.0)	21(100.0)	35(100.0)
Discontinued treatment	7(100.0)	7(100.0)	21(100.0)	35(100.0)
Discontinued study	7(100.0)	7(100.0)	21(100.0)	35(100.0)
Primary reason for end of treatment				
Abnormal test procedures	0(0.0)	0(0.0)	1(4.8)	1(2.9)
Adverse event(s)	2(28.6)	0(0.0)	1(4.8)	3(8.6)
Disease progression	5(71.4)	7(100.0)	15(71.4)	27(77.1)
New cancer therapy	0(0.0)	0(0.0)	1(4.8)	1(2.9)
Subject withdrew consent	0(0.0)	0(0.0)	3(14.3)	3(8.6)

Patient disposition by assigned dose level – oral arm (FAS)

	Schedule A	Schedule B		
	20mg N=6	15mg N=12	20mg N=3	All N=15
Treated with at least 1 dose	6(100.0	12(100.0)	3(100.0)	15(100.0)
Discontinued treatment	6(100.0)	12(100.0)	3(100.0)	15(100.0)
Discontinued study	6(100.0)	12(100.0)	3(100.0)	15(100.0)
Primary reason for end of treatment				
Adverse event(s)	0(0.0)	1(8.3)	0(0.0)	1(6.7)
Disease progression	5(83.3)	11(91.7)	3 (100.0)	14(93.3)
Subject withdrew consent	1(16.7)	0(0.0)	0(0.0)	0(0.0)

Baseline Characteristics

Demographic summary by assigned dose level – i.v. arm (FAS)

Demographic variable	10mg/m2 N=7	15mg/m2 N=7	20mg/m2 N=21	All N=35
Baseline age (years)				
n	7	7	21	35
Median	58.0	49.0	57.0	54.0
Min	35.0	33.0	37.0	33.0
Max	60.0	60.0	83.0	83.0
Baseline age category (years)				
<65	7(100.0)	7(100.0)	18(85.7)	32(91.4)
>=65	0(0.0)	0(0.0)	3(14.3)	3(8.6)
Race				
Black	0(0.0)	0(0.0)	1(4.8)	1(2.9)
Caucasian	7(100.0)	7(100.0)	17(81.0)	31(88.6)
Other	0(0.0)	0(0.0)	3(14.3)	3(8.6)

Baseline BSA (m^2)				
n	7	7	21	35
Median	1.6	1.9	1.8	1.8
Min	1.6	1.5	1.5	1.5
Max	1.8	2.1	2.2	2.2

Demographic summary by assigned dose level – oral arm (FAS)

Demographic variable	Schedule A 20mg N=6	Schedule B 15mg N=12	Schedule B 20mg N=3	All N=15
Baseline age (years)				
n	6	12	3	15
Median	54.5	53.5	47.0	52.0
Min	49.0	40.0	38.0	38.0
Max	59.0	65.0	60.0	65.0
Baseline age category (years)				
<65	6(100.0)	11(91.7)	3(100.0)	14(93.3)
>= 65	0(0.0)	1(8.3)	0(0.0)	1(6.7)
Race				
Caucasian	6(100.0)	12(100.0)	3(100.0)	15(100.0)
Baseline BSA (m^2)				
n	6	12	3	15
Mean	1.7	1.8	1.6	1.8
Min	1.6	1.5	1.5	1.5
Max	1.8	2.2	1.7	2.2

Outcome measures

Primary Outcome Result(s)

DLT in cycle 1 by assigned dose level – i.v. arm (MTD determining set)

	Escalation 10 mg/m2 N=7	Escalation 15 mg/m2 N=7	Escalation 20 mg/m2 N=14	Escalation 20 mg/m2 N=7	All N=35
No. patients in MTD determining set[1]	5(71.4)	7(100.0)	12(85.7)	6(85.7)	30(85.7)
No. patients with DLT			1(7.1)	1(14.3)	2(5.7)
DLT Event					
RENAL FAILURE				1(14.3)	1(2.9)
SEPSIS				1(14.3)	1(2.9)
GRADE 3 NEUTROPENIA ≥7 DAYS			1(7.1)		1(2.9)

- Based on CRF page “End of cycle one information”.

[1] Percentages are calculated relative to the FAS.

DLT in cycle 1 by assigned dose level – oral arm (MTD determining set)

	Schedule A	Schedule B		
	20 mg N=6	15 mg N=12	20 mg N=3	All N=15
No. patients in MTD determining set[1]	6(100.0)	12(100.0)	3(100.0)	15(100.0)
No. patients with DLT	1(16.7)	3(25.0)	1(33.3)	4(26.7)
DLT Event				
THROMBOCYTOPENIA[1] [2]		2(16.7)		2(13.3)
THROMBOCYTOPENIA GRADE 4[2]	1(16.7)		1(33.3)	1(6.7)
UNSTABLE ANGINA		1(8.3)		1(6.7)

- Based on CRF page “End of cycle one information”.

[1] CTCAE grade 3 thrombocytopenia for ≥7 consecutive days or re-occurring in the same cycle.

[2] DLTs fulfilling both thrombocytopenia criteria are displayed as thrombocytopenia grade 4.

The primary objective of the study to determine the MTD of i.v. and oral panobinostat in combination with trastuzumab was not fully reached due to the premature closure of the study for lack of efficacy.

Secondary Outcome Result(s)

Among all 56 patients, only 1 patient treated with 20 mg/m^2 in the i.v. arm had a confirmed PR lasting approximately 3 months.

PK data for the i.v. and oral panobinostat in combination with trastuzumab were in line with historical data of both drugs administered as a single agent, suggesting no apparent PK interaction.

Safety Results

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

AEs regardless of study drug relationship, by preferred term in ≥ 3 patients in individual assigned dose level – i.v. arm (Safety set)

	10mg/m2		15mg/m2		20mg/m2		All	
Preferred term	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
- Total	7(100)	2(28.6)	7(100)	2(28.6)	21(100)	12(57.1)	35(100)	16(45.7)
Nausea	4(57.1)		5(71.4)		14(66.7)		23(65.7)	
Headache	5(71.4)		6(85.7)		7(33.3)		18(51.4)	
Asthenia	5(71.4)		4(57.1)		4(19.0)		13(37.1)	
Dysgeusia	1(14.3)		1(14.3)		10(47.6)		12(34.3)	
Thrombocytopenia			1(14.3)		10(47.6)	8(38.1)	11(31.4)	8(22.9)
Diarrhoea	2(28.6)				9(42.9)	2(9.5)	11(31.4)	2(5.7)
Dyspnoea	1(14.3)		3(42.9)	1(14.3)	7(33.3)	1(4.8)	11(31.4)	2(5.7)
Fatigue	1(14.3)		3(42.9)		7(33.3)	1(4.8)	11(31.4)	1(2.9)

Muscle spasms	3(42.9)	2(28.6)		6(28.6)		11(31.4)	
Vomiting	1(14.3)	2(28.6)		7(33.3)	1(4.8)	10(28.6)	1(2.9)
Cough	2(28.6)	1(14.3)		7(33.3)		10(28.6)	
Stomatitis	2(28.6)	2(28.6)		5(23.8)		9(25.7)	
Decreased appetite				8(38.1)	1(4.8)	8(22.9)	1(2.9)
Neutropenia	1(14.3)	3(42.9)	1(14.3)	3(14.3)	1(4.8)	7(20.0)	2(5.7)
Bone pain	2(28.6)	1(14.3)		3(14.3)		6(17.1)	
Dizziness		1(14.3)		5(23.8)		6(17.1)	
Anaemia		1(14.3)		4(19.0)	1(4.8)	5(14.3)	1(2.9)
Blood creatinine increased	3(42.9)	1(14.3)		1(4.8)	1(4.8)	5(14.3)	1(2.9)
Abdominal pain	1(14.3)	1(14.3)		3(14.3)		5(14.3)	
Arthralgia	1(14.3)	1(14.3)		3(14.3)		5(14.3)	
Back pain		1(14.3)		4(19.0)		5(14.3)	
Chills		2(28.6)		3(14.3)		5(14.3)	
Constipation		1(14.3)		4(19.0)		5(14.3)	
Influenza like illness				5(23.8)		5(14.3)	
Pyrexia	1(14.3)	1(14.3)		3(14.3)		5(14.3)	
Hypokalemia		1(14.3)		3(14.3)	2(9.5)	4(11.4)	2(5.7)
Dry mouth				4(19.0)		4(11.4)	
Oedema peripheral				4(19.0)		4(11.4)	
Dehydration				3(14.3)	2(9.5)	3(8.6)	2(5.7)
Contusion				3(14.3)		3(8.6)	
Dyspepsia				3(14.3)		3(8.6)	
Nasopharyngitis				3(14.3)		3(8.6)	
Urinary tract infection				3(14.3)		3(8.6)	

AEs regardless of study drug relationship, by preferred term in ≥ 2 patients in individual assigned dose level in Schedule A or B - oral arm (Safety set)

	Schedule A				**Schedule B**			
	20 mg		**15 mg**		**20 mg**		**All**	
	N=6		**N=12**		**N=3**		**N=15**	
Preferred term	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**	**Any grade**	**Grade 3/4**
- Total	6(100)	3(50.0)	12(100)	8(66.7)	3(100)	1(33.3)	15(100)	9(60.0)
Diarrhoea	3(50.0)		7(58.3)	2(16.7)	2(66.7)		9(60.0)	2(13.3)
Thrombocytopenia	3(50.0)	1(16.7)	5(41.7)	3(25.0)	2(66.7)	1(33.3)	7(46.7)	4(26.7)
Neutropenia	1(16.7)		5(41.7)	1(8.3)	1(33.3)		6(40.0)	1(6.7)
Headache			5(41.7)		1(33.3)		6(40.0)	
Nausea	4(66.7)		4(33.3)		2(66.7)		6(40.0)	
Fatigue	2(33.3)		5(41.7)	1(8.3)			5(33.3)	1(6.7)
Decreased appetite			4(33.3)	1(8.3)			4(26.7)	1(6.7)
Back pain	1(16.7)		4(33.3)				4(26.7)	
Constipation	1(16.7)		4(33.3)				4(26.7)	

Dyspepsia	1(16.7)		3(25.0)		1(33.3)	4(26.7)	
Pyrexia	2(33.3)	1(16.7)	3(25.0)	1(8.3)		3(20.0)	1(6.7)
Asthenia	3(50.0)		1(8.3)		2(66.7)	3(20.0)	
Cough			3(25.0)			3(20.0)	
Dry mouth			3(25.0)			3(20.0)	
Epistaxis			3(25.0)			3(20.0)	
Leukopenia	1(16.7)	1(16.7)	2(16.7)		1(33.3)	3(20.0)	
Pruritus			3(25.0)			3(20.0)	
Vomiting	3(50.0)		2(16.7)		1(33.3)	3(20.0)	
Abdominal pain			2(16.7)			2(13.3)	
Dry skin			2(16.7)			2(13.3)	
Dysgeusia			2(16.7)			2(13.3)	
Dyspnoea			2(16.7)			2(13.3)	
Lymphoedemas			2(16.7)			2(13.3)	
Abdominal pain upper	2(33.3)		1(8.3)			1(6.7)	
Arthralgia	2(33.3)						

Serious Adverse Events and Deaths

Summary of AE categories in the study – i.v. arm (Safety set)

	10 mg/m^2 N=7	15 mg/m^2 N=7	20 mg/m^2 N=21	All N=35
Serious or other significant event				
Deaths[1] (on treatment)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Grade 3-4 AEs	2(28.6)	2(28.6)	12(57.1)	16(45.7)
All serious AEs	3(42.9)	1(14.3)	5(23.8)	9(25.7)
Study-drug-related SAEs	0(0.0)	0(0.0)	3(14.3)	3(8.6)
AE leading to discontinuation[2]	2(28.6)	0(0.0)	1(4.8)	3(8.6)

[1]AEs or deaths occurring more than 28 days after discontinuation of study treatment are not summarized.
[2]As reported on AE CRF page

Summary of AE categories in the study – oral arm (Safety set)

	Schedule A		Schedule B	
	20 mg N=6	15 mg N=12	20 mg N=3	All N=15
Serious or other significant event				
Deaths[1] (on treatment)	1(16.7)	0(0.0)	0(0.0)	0(0.0)
Grade 3-4 AEs	3(50.0)	8(66.7)	1(33.3)	9(60.0)
All serious AEs	3(50.0)	2(16.7)	1(33.3)	3(20.0)
Study-drug-related SAEs	1(16.7)	1(8.3)	1(33.3)	2(13.3)
AE leading to discontinuation[2]	0(0.0)	1(8.3)	0(0.0)	1(6.7)

[1]AEs or deaths occurring more than 28 days after discontinuation of study treatment are not summarized.
[2]As reported on AE CRF page

Cardiac safety

Number and percentage of patients with notable QTcF interval values by assigned dose level – i.v. arm (Safety set)

	10 mg/m2 N=7	15 mg/m2 N=7	20 mg/m2 N=21	All N=35
Maximum QTcF value				
Number of patients[1]	7(100)	7(100)	21(100)	35(100)
>480 ms and <= 500 ms	1(14.3)		1(4.8)	2(5.7)
>500 ms				
Maximum QTcF increase from baseline				
Number of patients[2]	7(100)	7(100)	21(100)	35(100)
>30 ms and <= 60 ms	2(28.6)	2(28.6)	4(19.0)	8(22.9)
>60 ms	1(14.3)		1(4.8)	2(5.7)

[1] Number of patients with at least one post-baseline measurement;

[2] Number of patients with a measurement at both baseline and post-baseline. Baseline is defined as the average of all pre-treatment ECGs on day 1 visit.

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

	Schedule A 20 mg N=6	Schedule B 15 mg N=12	Schedule B 20 mg N=3	Schedule B All N=15
Maximum QTcF value				
Number of patients[1]	6(100)	12(100)	3(100)	15(100)
>480 ms and <= 500 ms				
>500 ms				
Maximum QTcF increase from baseline				
Number of patients[2]	6(100)	12(100)	3(100)	15(100)
>30 ms and <= 60 ms	1(16.7)	3(25.0)		3(20.0))
>60 ms				

[1] Number of patients with at least one post-baseline measurement;

[2] Number of patients with a measurement at both baseline and post-baseline. Baseline is defined as the average of all pre-treatment ECGs on day 1 visit.

The safety profile of study treatment combination in HER2 positive MBC did not indicate any clinically relevant increase in AEs incidence and/or the occurrence of new toxicities compared to each component of the tested regimen.

Other Relevant Findings

None

Date of Clinical Trial Report 08-Mar-2012
Date Inclusion on Novartis Clinical Trial Results Database
Date of Latest Update