Sponsor

Novartis

Generic Drug Name

Trial Indication(s)

HER2 negative, inoperable locally advanced or metastatic breast cancer

Protocol Number

Protocol no. CBEZ235B2101; EudraCT no. 2011-002400-32

Protocol Title

A dose-finding Phase Ib study followed by an open-label, randomized Phase II study of BEZ235 plus paclitaxel in patients with HER2 negative, inoperable locally advanced or metastatic breast cancer

Clinical Trial Phase

Phase Ib/II

Phase of Drug Development

Phase II

Study Start/End Dates

30-Jan-2012 to 19-May-2014

Reason for Termination (If applicable)

The study did not meet Phase Ib primary objective to establish the maximum tolerated dose/ recommended dose for Phase II (MTD/RP2D) of twice daily BEZ235 in combination with weekly paclitaxel. Hence, Novartis terminated the study during the Phase Ib and the Phase II part of the study was not conducted.

Study Design/Methodology

This was a multi-center, open-label, dose-finding, Phase Ib followed by a randomized Phase II study in patients with HER2 negative locally advanced breast cancer or metastatic breast cancer. Phase Ib was a dose escalation study and was to investigate the MTD and/or RP2D of oral twice daily (bid) BEZ235 in combination with weekly paclitaxel based on dose limiting toxicity (DLT) observed during the first cycle using a Bayesian logistic regression model (BLRM) with overdose control. The starting dosage for BEZ235 was 200 mg bid (400 mg

total daily dose). Paclitaxel was administered at a fixed weekly dose of 80 mg/m^2. Patients were to receive bid dosing of BEZ235 together with weekly paclitaxel infusions until disease progression or until pre-defined discontinuation criteria were met.

Once the MTD and/or RP2D had been declared, Phase II of the study was to randomize patients to either twice daily oral BEZ235 in combination with weekly paclitaxel infusions or with weekly paclitaxel infusions alone, and assess the treatment effect on progression free survival (PFS).

Centers

Three centers (two in France and one in Spain).

Publication

None

Objectives:

Phase Ib:

Primary objective:

- To determine the MTD and/or RP2D of oral twice daily BEZ235 in combination with weekly (qw) paclitaxel in patients with HER2 negative metastatic or inoperable, locally advanced breast cancer.

Secondary objectives:

- To assess the safety and tolerability of BEZ235/paclitaxel combination therapy.
- To assess the preliminary activity of BEZ235/paclitaxel combination therapy.

Phase II:

Primary objective:

- To estimate the treatment effect of BEZ235/paclitaxel combination therapy versus paclitaxel alone in HER2 negative patients with first line metastatic or inoperable locally advanced breast cancer.

Secondary objectives:

- To estimate the treatment effect of BEZ235/ paclitaxel combination therapy versus paclitaxel alone according to PI3K activation status.
- To estimate the treatment effect of BEZ235/ paclitaxel combination therapy versus paclitaxel alone.
- To evaluate additional efficacy parameters of BEZ235/ paclitaxel combination therapy versus paclitaxel alone.
- To evaluate safety and tolerability of BEZ235/ paclitaxel combination therapy versus paclitaxel alone.

The study did not meet its primary objective to establish the MTD/RP2D of BEZ235 in combination with paclitaxel. Consequently, the Phase II part of the study was not conducted.

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

BEZ235 was administered orally on a continuous twice daily dosing schedule (starting dose 200 mg bid) together with a fixed dose (80 mg/m^2) of weekly paclitaxel i.v.

Statistical Methods

- An adaptive five-parameter Bayesian logistic regression model (BLRM) with overdose control was used to guideBEZ235 dose selection and determination of the MTD and/or RP2D. The applied adaptive BLRM provided estimates for the probability of observing DLT in Cycle 1 at a given dose level. Typically the MTD was to be the dose with the highest probability of being in the targeted toxicity range (DLT rate between 16%-35%) among the doses fulfilled the overdose criteria (less than 25% chance of excessive toxicity).
- The assessment of safety was based mainly on the frequency and severity of adverse events and on the number of laboratory values that fall outside of pre-determined ranges. Other safety data (e.g. electrocardiogram, vital signs) were considered as appropriate.
- The efficacy endpoints included Progression Free Survival (PFS), Overall response rate (ORR) and clinical benefit rate (CBR) using RECIST.
- As the study enrollment was terminated prior to the determination of MTD/RP2D, and the study results were given in an abbreviated report, progression free survival was not summarized.
- Based on the patients' best overall response during the study, the following rates were calculated.
    - ORR defined as the proportion of patients with a best overall response of complete response or partial response,
    - CBR defined as the proportion of patients with a best overall response of complete response, partial response or Non- complete response /Non-progressive disease or stable disease with duration of 24 weeks or longer.
- Analyses of best overall response and response rates were performed based on the full analysis set. The rates were provided overall and by dose level. Generally, corresponding exact 95% confidence intervals were presented overall.

Study Population: Key Inclusion/Exclusion Criteria

Patients included (Phase Ib) who met the following key criteria:

- Patient is a female ≥ 18 years of age.
- Patient has HER2-negative, inoperable locally advanced or metastatic breast cancer.
- Patient has adequate bone marrow and organ function.

Patients excluded (Phase Ib) who met the following key criteria:

- Patient has received previous treatment with PI3K and/or mTOR pathway inhibitors.
- Patient has active uncontrolled or symptomatic central nervous system (CNS) metastases.
- Patient has not recovered from side effects of previous therapy.
- Patient has active cardiac disease or a history of cardiac dysfunction.
- Patient has a family history of congenital long or short QT, or known history of QT/QTc prolongation or Torsades de Pointes (TdP).
- Patient has inadequately controlled hypertension (i.e., SBP>180 mmHg or DBP>100 mmHg).
- Patient has uncontrolled diabetes mellitus.
- Patient has impairment of GI function or GI disease that may significantly alter the absorption of BEZ235 and/ or paclitaxel.

Participant Flow Table

Patient disposition (Full analysis set)

	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80	Total
	N=5	N=13	N=18
Disposition reason	**n (%)**	**n (%)**	**n (%)**
Patients treated			
End of treatment	5 (100)	13 (100)	18 (100)
Primary reason for end of treatment phase			
Adverse event	2 (40.0)	3 (23.1)	5 (27.8)
Physician decision	0	1 (7.7)	1 (5.6)
Progressive disease	3 (60.0)	8 (61.5)	11 (61.1)
Subject/guardian decision	0	1 (7.7)	1 (5.6)
Study evaluation after end of treatment			
Patients no longer being followed for study evaluation	5 (100)	12 (92.3)	17 (94.4)
Patients continuing to be followed for study evaluation	0	1 (7.7)	1 (5.6)
Primary reason for study evaluation phase completion			
New therapy for study indication	0	1 (7.7)	1 (5.6)

Baseline Characteristics

Demographic summary (Full analysis set)

	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80	Total
	N=5	N=13	N=18
Age Group, n(%)			
<65 years	5 (100)	11 (84.6)	16 (88.9)
≥ 65 years	0	2 (15.4)	2 (11.1)
Age (years)			
n	5	13	18
mean	43.0	53.1	50.3
SD	8.03	11.77	11.60
min	32	36	32
median	47.0	52.0	50.5
max	50	81	81
Race, n(%)			
Caucasian	5 (100)	13 (100)	18 (100)
BSA (m^2)			
n	5	13	18
mean	1.72	1.74	1.73
SD	0.118	0.139	0.130
min	1.6	1.5	1.5
median	1.71	1.76	1.74
max	1.9	1.9	1.9
ECOG performance status, n (%)			
0	1 (20.0)	3 (23.1)	4 (22.2)
1	4 (80.0)	10 (76.9)	14 (77.8)

BSA = Body Surface Area; SD = Standard Deviation; ECOG = Eastern Cooperative Oncology Group

Summary of Efficacy

Primary Outcome Result(s)

Summary of posterior distribution of DLT rates at end of study (Dose-determining set)

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
BEZ235 Dose (mg)	0-0.16	0.16-0.35	0.35-1	Mean	SD	2.5%	50%	97.5%
100	0.379	0.537	0.084	0.203	0.098	0.052	0.190	0.424
200	0.189	0.673	0.137	0.245	0.094	0.091	0.236	0.452
300	0.077	0.680	0.242	0.287	0.094	0.125	0.279	0.489
400	0.037	0.570	0.393	0.327	0.102	0.148	0.321	0.540

	Posterior probabilities that Pr(DLT) is in interval:					Quantiles		
BEZ235 Dose (mg)	0-0.16	0.16-0.35	0.35-1	Mean	SD	2.5%	50%	97.5%
600	0.016	0.353	0.632	0.403	0.130	0.175	0.395	0.674
800	0.013	0.244	0.743	0.467	0.161	0.186	0.459	0.795

Dose limiting toxicities during the first 28 days of treatment by primary system organ class, preferred term (Dose-determining set)

Primary system organ class Preferred Term	BEZ235 100 mg bid + P80 N=5 n (%)	BEZ235 200 mg bid + P80 N=12 n (%)	Total N=17 n (%)
Number of patients with at least one DLT	1 (20.0)	5 (41.7)	6 (35.3)
Blood and lymphatic system disorders	**1 (20.0)**	**2 (16.7)**	**3 (17.6)**
Neutropenia	1 (20.0)	2 (16.7)	3 (17.6)
Gastrointestinal disorders	**0**	**4 (33.3)**	**4 (23.5)**
Stomatitis	0	3 (25.0)	3 (17.6)
Nausea	0	2 (16.7)	2 (11.8)
Vomiting	0	1 (8.3)	1 (5.9)

Secondary Outcome Result(s)

Best overall response summary table as per Investigator, by dose level (FAS)

	BEZ235 100 mg bid + P80 N=5		BEZ235 200 mg bid + P80 N=13		Total N=18	
	n (%)	(95% CI)	n (%)	(95% CI)	n (%)	(95% CI)
Patients with measurable disease at baseline	5 (100)		10 (76.9)		15 (83.3)	
Patients with non-measurable disease only at baseline	0		3 (23.1)		3 (16.7)	
Best overall response						
Partial response (PR)	1 (20.0)		2 (15.4)		3 (16.7)	
Non-CR/Non-PD	0		2 (15.4)		2 (11.1)	
Stable disease (SD)	4 (80.0)		2 (15.4)		6 (33.3)	
Progressive disease (PD)	0		4 (30.8)		4 (22.2)	
Unknown (UNK)	0		3 (23.1)		3 (16.7)	
Overall response rate (ORR:CR+PR)	1 (20.0)	(0.5, 71.6)	2 (15.4)	(1.9, 45.4)	3 (16.7)	(3.6, 41.4)
Clinical benefit rate (CBR: CR+PR+SD+Non-CR/Non-PD >24 weeks)	3 (60.0)	(14.7, 94.7)	3 (23.1)	(5.0, 53.8)	6 (33.3)	(13.3, 59.0)

N: The total number of patients in the dose level. It is the denominator for percentage (%) calculation.
n: Number of patients who are at the corresponding category.
Note: The 95% CI for the frequency distribution of each variable were computed using Clopper-Pearson method if there is sufficient data.

Summary of Safety

Treatment-emergent adverse events (incidence in at least 50% of the patients by overall frequency of SOC and incidence in at least 20% of the patients by overall frequency of PT) regardless of study treatment relationship, by primary SOC, PT and maximum grade (Safety set)

	BEZ235 100 mg bid + P80 N=5		BEZ235 200 mg bid + P80 N=13		Total N=18	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Any adverse event	**5 (100)**	**4 (80.0)**	**13 (100)**	**8 (61.5)**	**18 (100)**	**12 (66.7)**
Blood and lymphatic system disorders	**4 (80.0)**	**2 (40.0)**	**12 (92.3)**	**3 (23.1)**	**16 (88.9)**	**5 (27.8)**
Neutropenia	3 (60.0)	2 (40.0)	10 (76.9)	3 (23.1)	13 (72.2)	5 (27.8)
Anaemia	2 (40.0)	1 (20.0)	5 (38.5)	0	7 (38.9)	1 (5.6)
Gastrointestinal disorders	**5 (100)**	**1 (20.0)**	**13 (100)**	**5 (38.5)**	**18 (100)**	**6 (33.3)**
Nausea	5 (100)	0	11 (84.6)	1 (7.7)	16 (88.9)	1 (5.6)
Diarrhoea	3 (60.0)	1 (20.0)	10 (76.9)	2 (15.4)	13 (72.2)	3 (16.7)
Stomatitis	2 (40.0)	0	10 (76.9)	3 (23.1)	12 (66.7)	3 (16.7)
Vomiting	3 (60.0)	0	7 (53.8)	0	10 (55.6)	0
Abdominal pain upper	2 (40.0)	0	4 (30.8)	0	6 (33.3)	0
Constipation	2 (40.0)	0	4 (30.8)	0	6 (33.3)	0
Gastrooesophageal reflux disease	0	0	4 (30.8)	0	4 (22.2)	0
General disorders and administration site conditions	**5 (100)**	**1 (20.0)**	**10 (76.9)**	**2 (15.4)**	**15 (83.3)**	**3 (16.7)**
Asthenia	5 (100)	1 (20.0)	9 (69.2)	2 (15.4)	14 (77.8)	3 (16.7)
Pyrexia	2 (40.0)	0	2 (15.4)	0	4 (22.2)	0
Infections and infestations	**3 (60.0)**	**0**	**8 (61.5)**	**0**	**11 (61.1)**	**0**
Investigations	**3 (60.0)**	**2 (40.0)**	**6 (46.2)**	**1 (7.7)**	**9 (50.0)**	**3 (16.7)**
Gamma-glutamyltransferase increased	3 (60.0)	2 (40.0)	1 (7.7)	1 (7.7)	4 (22.2)	3 (16.7)
Weight decreased	0	0	4 (30.8)	0	4 (22.2)	0
Metabolism and nutrition disorders	**4 (80.0)**	**0**	**11 (84.6)**	**1 (7.7)**	**15 (83.3)**	**1 (5.6)**
Decreased appetite	4 (80.0)	0	7 (53.8)	0	11 (61.1)	0
Hypercholesterolaemia	2 (40.0)	0	2 (15.4)	0	4 (22.2)	0

	BEZ235 100 mg bid + P80 N=5		BEZ235 200 mg bid + P80 N=13		Total N=18	
	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)	All grades n (%)	Grade 3/4 n (%)
Musculoskeletal and connective tissue disorders	**4 (80.0)**	**0**	**6 (46.2)**	**0**	**10 (55.6)**	**0**
Myalgia	3 (60.0)	0	4 (30.8)	0	7 (38.9)	0
Arthralgia	3 (60.0)	0	3 (23.1)	0	6 (33.3)	0
Nervous system disorders	**4 (80.0)**	**1 (20.0)**	**7 (53.8)**	**1 (7.7)**	**11 (61.1)**	**2 (11.1)**
Paraesthesia	1 (20.0)	1 (20.0)	4 (30.8)	1 (7.7)	5 (27.8)	2 (11.1)
Respiratory, thoracic and mediastinal disorders	**3 (60.0)**	**1 (20.0)**	**9 (69.2)**	**1 (7.7)**	**12 (66.7)**	**2 (11.1)**
Epistaxis	1 (20.0)	0	7 (53.8)	0	8 (44.4)	0
Cough	1 (20.0)	0	3 (23.1)	0	4 (22.2)	0
Skin and subcutaneous tissue disorders	**3 (60.0)**	**0**	**10 (76.9)**	**2 (15.4)**	**13 (72.2)**	**2 (11.1)**
Dry skin	0	0	6 (46.2)	0	6 (33.3)	0
Rash	2 (40.0)	0	4 (30.8)	0	6 (33.3)	0
Onycholysis	2 (40.0)	0	3 (23.1)	0	5 (27.8)	0
Alopecia	0	0	4 (30.8)	0	4 (22.2)	0
Pruritus	1 (20.0)	0	3 (23.1)	0	4 (22.2)	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency, as reported in the total All grades column.

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

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

MedDRA Version 17.0 has been used for the reporting.

Summary of deaths and adverse events (Safety set)

	BEZ235 100 mg bid + P80 N=5 n (%)	BEZ235 200 mg bid + P80 N=13 n (%)	Total N=18 n (%)
Patients with at least one AE	5 (100)	13 (100)	18 (100)
Patients with at least one SAE, regardless of relationship to study treatment	3 (60.0)	5 (38.5)	8 (44.4)
Patients with at least one SAE, with suspected relationship to study treatment	1 (20.0)	5 (38.5)	6 (33.3)
Treatment-emergent death	0	0	0

	BEZ235 100 mg bid + P80	BEZ235 200 mg bid + P80	Total
	N=5	N=13	N=18
	n (%)	n (%)	n (%)
Grade 3-4 AE regardless of relationship to study treatment [a]	4 (80.0)	8 (61.5)	12 (66.7)
Grade 3-4 AE with suspected relationship to study treatment [a]	4 (80.0)	8 (61.5)	12 (66.7)
Patients who discontinued from study treatment due to SAEs [a]	0	1 (7.7)	1 (5.6)
Patients who discontinued from study treatment due to non-serious AEs [a]	4 (80.0)	4 (30.8)	8 (44.4)

[a] Adverse events occurring more than 30 days after last date of study treatment are not summarized.

Other Relevant Findings

Not applicable

Conclusion:

- The study did not meet its primary objective to establish the MTD/ RP2D of twice daily BEZ235 in combination with weekly paclitaxel; based on the observed dose limiting toxicities, 100 mg bid was considered an acceptable dose level while 200 mg bid did not meet the overdose criteria per the BLRM; no other doses have been explored and the Phase II part was not conducted.
- Pharmacokinetic analysis showed there was high inter and intra patient variability associated with BEZ235 200 mg bid and 100 mg bid, and lack of evidence for a relation between BEZ235 plasma concentrations and pAKT inhibition. The pharmacokinetic data did not further suggest any pharmacokinetic interaction between BEZ235 and paclitaxel, however firm conclusions are not possible due to the limited number of patients.
- The overall safety profile of BEZ235 twice daily in combination with paclitaxel in this study was consistent with previous studies and with the expected toxicities of each compound as single agent; no new or unexpected safety findings have been made. Gastrointestinal disorders (e.g. stomatitis, diarrhea and nausea/vomiting) as well as hematologic disorders (e.g. neutropenia) were among the most common adverse events, and also dose limiting toxicities.
- Three out of 18 patients achieved a partial response, however, given the Phase II part was not conducted no firm conclusion are possible with regards to the clinical benefit of adding BEZ235 to paclitaxel.

Date of Clinical Trial Report

11-Dec-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

22-Apr-2015

Date of Latest Update

Not applicable

Reason for Update

Not applicable