Sponsor

Novartis Pharmaceuticals

Generic Drug Name

BEZ235

Therapeutic Area of Trial

Breast Cancer

Approved Indication

Investigational

Protocol Number

CBEZ235B2203

Title

A Phase Ib/randomized Phase II study of BEZ235 and trastuzumab versus lapatinib and capecitabine in patients with HER2-positive locally advanced or metastatic breast cancer who failed prior trastuzumab.

Study Phase

Phase Ib/II

Study Start/End Dates

17-Feb-2012 to 28-Jun-2012

Study Design/Methodology

This was a multi-center, open-label Phase Ib/randomized Phase II study in patients with HER2 positive locally advanced breast cancer (LABC) or metastatic breast cancer (MBC). Phase Ib was a dose escalation study and was to investigate the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of oral twice daily BEZ235 in combination with weekly fixed dose of trastuzumab based on DLT using a BLRM with overdose control. The starting dosage for BEZ235 was 400 mg/d (200 mg bid). Trastuzumab was administered at a fixed weekly dose of 2 mg/kg as per approved dosage and administration. Once the MTD and/or RP2D had been declared, Phase II of the study was to randomize patients who had failed prior trastuzumab to receive BEZ235 plus trastuzumab or capecitabine plus lapatinib and assess the treatment effect on progression free survival (PFS).

The Phase II part of the study was not conducted since the MTD/RP2D of BEZ235 in combination with trastuzumab has not been established and the study closed consequently.

Centers

Three enrolling centers in two countries: United Kingdom (2), Spain (1)

Publication

None

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

BEZ235 was administered orally on a continuous twice daily dosing schedule at increasing doses (starting dose 200 mg bid) together with a fixed dose (2 mg/kg) of weekly trastuzumab (loading dose of 4 mg/kg on Cycle 1 Day 1 if required (as assessed by the Investigator).

Statistical Methods

Analysis of primary variable

Incidence of DLTs in first cycle: DLT is defined as treatment-related toxicity (classified according to the Common Toxicity Criteria for Adverse Events (CTCAE) Version 4) occurring during the first 28 treatment days and meeting specific protocol-predefined criteria. The information was integrated in a BLRM with overdose control to estimate the maximum tolerated dose. An adaptive five-parameter BLRM was used during the dose escalation phase for the BEZ235 dose level selection and for determination of the MTD and/or RP2D of the combination. Summary of posterior distribution of DLT rates and corresponding figures: dose response curve (DLT probability median and its 95%CI) and inference results (probabilities of under dosing, targeted toxicity and overdosing) was provided by dose level at the end of study.

Analysis of secondary variables

Efficacy: The endpoints included: PFS, overall response rate (ORR), clinical benefit rate (CBR); complete response (CR) or partial response (PR) or stable response (SD)>24 weeks. Data collected on Response Evaluation Criteria In Solid Tumors (RECIST) assessments and responses were listed; no PFS or response rate was derived.

Safety: 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.

Pharmacokinetics: No summary statistics and PK analysis was performed. Pre-and post-dose concentrations of BEZ235 and trastuzumab were listed.

Study Population: Inclusion/Exclusion Criteria and Demographics

Key inclusion criteria

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

- Females with confirmed histological and/or cytological diagnosis of invasive breast cancer with locally advanced or metastatic disease and measurable/or non-measurable as per RECIST 1.1.
- HER2-positive disease defined by fluorescent in situ hybridization (FISH) or chromogenic in situ hybridization (CISH) or Immunohistochemistry (IHC) (3+ staining) by local laboratory testing;
- Aged ≥ 18 years.
- No more than three prior cytotoxic chemotherapy lines; prior treatment with trastuzumab (alone or in combination).
- Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 or 2),
- Adequate bone marrow and organ function (e.g. absolute neutrophil count ≥ $1.5x10^9$/L, platelets ≥ $100x10^9$/L, hemoglobin (Hgb) ≥ 9.0 g/dL, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 x upper limit of normal (ULN) (or ≤ 5.0xULN if liver metastases are present), serum creatinine ≤ 1.5xULN, fasting plasma glucose (FPG) ≤ 140mg/dL (7.8 mmol/L), HbA1c ≤ 8%.

Key exclusion criteria

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

- Uncontrolled or symptomatic central nervous system (CNS) metastases.
- Previous treatment with PI3K and/or mTOR pathway inhibitors, not recovered from side effects of previous therapies.
- Known hypersensitivity, intolerance and/or contraindications to any of the study medications.
- Malignancy within the last 3 years before study enrollment.
- History or active severe and/or uncontrolled cardiac conditions that could affect the participation in the study.
- Inadequately controlled hypertension or diabetes mellitus, impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BEZ235.
- Systemic high dose steroids or another immuno-suppressive agents; moderate and strong inhibitors or inducers of isoenzyme CYP3A4, drugs with a known risk to induce Torsades de Pointes, warfarin, and coumadin analogues; immuno-compromised patients including known seropositivity for HIV.
- Other concurrent severe and /or uncontrolled medical condition that, in the Investigator's judgment contraindicated participation in the clinical study; pregnant or nursing (lactating) women.

Participant Flow

Patient disposition (Full analysis set)

Disposition reason	BEZ235 200 mg bid plus trastuzumab N=5 n (%)
Patients treated	
Treatment ongoing*	0
End of treatment	5 (100)
Primary reason for end of treatment phase	
Adverse event(s)	3 (60.0)
Disease progression	2 (40.0)
Study evaluation after end of treatment	
Patients no longer being followed for study evaluation	2 (40.0)
Patients continuing to be followed for study evaluation	3 (60.0)
Primary reason for study evaluation phase completion	
New therapy for study indication	3 (60.0)

*Patients ongoing at the time of the cut-off 07-Dec-2012

Baseline Characteristics

Demographic summary (Full analysis set)

Disposition reason	BEZ235 200 mg bid plus trastuzumab N=5 n (%)
Age group, n (%)	
<65 years	5 (100)
≥ 65 years	0
Age (years)	
n	5
Mean (SD)	52.4 (9.66)
Median	57
Min-Max	38-60
Race, n (%)	
Caucasian	5 (100)
Body mass index (kg/m^2)	
n	5
Mean (SD)	27.18 (5.17)
Median	24.8
Min-Max	22.2-34.0
ECOG performance status, n (%)	
0	4 (80.0)
1	1 (20.0)

Outcome measures

Primary Outcome Result(s)

Three out of five patients in the first cohort experienced a DLT. No additional cohorts/dose levels were explored, and the MTD/RP2D has not been established.

Secondary Outcome Result(s)

RECIST overall lesion response as per investigator (Full analysis set)

Overall response	BEZ235 200 mg bid plus trastuzumab N=5 n (%)
Stable disease	3 (60%)
Progressive disease	2 (40%)

List of figures

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Safety Results

Adverse Events by System Organ Class

Primary system organ class	BEZ235 200 mg bid plus trastuzumab N=5 n (%)
Any AE	5 (100.0)
Gastrointestinal disorders	5 (100.0)
Nervous system disorders	3 (60.0)
Psychiatric disorders	3 (60.0)
Respiratory, thoracic and mediastinal disorders	3 (60.0)
Skin and subcutaneous tissue disorders	3 (60.0)
Investigations	2 (40.0)
Metabolism and nutrition disorders	2 (40.0)
General disorders and administration site conditions	1 (20.0)
Musculoskeletal and connective tissue disorders	1 (20.0)
Reproductive system and breast disorders	1 (20.0)

Most Frequently Reported AEs Overall by Preferred Term (reported in at least ≥ 40% (two patients))

Preferred term	BEZ235 200 mg bid plus trastuzumab N=5 All grades n (%)	BEZ235 200 mg bid plus trastuzumab N=5 Grade 3/4 n (%)
Total	**5 (100)**	**3 (60.0)**
Stomatitis	4 (80.0)	3 (60.0)
Diarrhea	3 (60.0)	0
Nausea	3 (60.0)	0
Decreased appetite	2 (40.0)	0
Lethargy	2 (40.0)	0

Serious Adverse Events and Deaths

Category	BEZ235 200 mg bid plus trastuzumab N=5 n (%)
Patients with at least one AE	5 (100)
Patients with at least one SAE, regardless of relationship to study treatment	2 (40.0)
Patients with at least one SAE, with suspected relationship to study treatment	0
Patients who died	0
Treatment-emergent death [1]	0
Patients who discontinued from study due to AEs	3 (60.0)
Discontinued study treatment due to SAEs	0
Discontinued study treatment due to non-serious AEs	3 (60.0)

Categories are not mutually exclusive

[1] On-treatment deaths are deaths which occurred up to 30 days after last date of exposure to study treatment

[2] Adverse events occurring more than 30 days after last date of exposure to study treatment are not summarized

Other Relevant Findings

None

Date of Clinical Trial Report

12-Apr-2013

Date Inclusion on Novartis Clinical Trial Results Database

29-Apr-2013

Date of Latest Update