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 to trastuzumab.

Published: 13-12-2011
Last updated: 30-04-2024

PrimairTo determine the MTD and/or RP2D of oral twice daily (BID) BEZ235 in combination with trastuzumab in patients with HER2-positive breast cancerSecondairTo assess the preliminary activity of the combinationTo assess the safety and tolerability…

Ethical review	Approved WMO
Status	Will not start
Health condition type	Miscellaneous and site unspecified neoplasms benign
Study type	Interventional

Summary

ID

NL-OMON35443

Source
ToetsingOnline

Brief title
Ib/II BEZ235+trastuzumab vs lapatinib+capecitabine HER2+ MBC

Condition

- Miscellaneous and site unspecified neoplasms benign

Synonym
breastcancer

Research involving

Human

Sponsors and support

Primary sponsor: Novartis
Source(s) of monetary or material Support: Novartis Pharma B.V.

Intervention

Keyword: - BEZ235 / trastuzumab, - HER2-positive locally advanced/metastatic breastcancer, - phase Ib/randomized phase II, - PI3K- and mTOR inhibitors

Outcome measures

Primary outcome

Incidence of DLTs in the first cycle

Secondary outcome

Secundary

Progression Free Survival (PFS)

Overall Response Rate (ORR)

Clinical Benefit Rate (CBR; CR or PR or SD> 24 weeks)

Frequency and severity of adverse events; other safety data as considered

appropriate

BEZ235 plasma and trastuzumab serum concentrations

Exploratory

Levels of markers of glucose metabolism

Levels of pAKT, p4EBP1 and pS6 in peripheral blood mononuclear cell (PBMC)

Mutation, loss and/or amplification of K-ras, PIK3CA, PTEN etc. in tissue

Study description

Background summary

Breast cancer, after skin carcinomas, is the most common malignancy and the leading cause of cancer mortality in women worldwide. In the US, it is estimated that approximately 207,090 new cases of invasive breast cancer were diagnosed in 2010. For the same year about 40,230 women died from their disease (American Cancer Society 2010). Approximately 40% of diagnosed patients will eventually develop metastatic breast cancer (MBC). Metastatic breast cancer is still considered incurable, and treatment is palliative. Despite the variety of agents available for the treatment of MBC, the median survival time for women with MBC is about 2 to 3 years, and only 20% of women will be alive 5 years after diagnosis (Gennari 2005, Miles 2009). As a result, the goals of treatment are to optimize quality of life, manage symptoms and prolong survival.

Over the past years, progress has been made in understanding the molecular biology and genetics of breast cancer which are central to the development of novel therapies. Among others, the phosphatidylinositol-3-kinase (PI3K) pathway has been identified as an important target. The PI3K pathway is a key signal transduction system linking multiple oncogenes, tumor suppressors and receptor classes to essential cellular functions such as cell growth, survival, motility and metabolism (reviewed in (Courtney et al 2010)). Important components of the signaling cascade include pAKT, mTOR, and PTEN as a negative regulator of PI3K

In HER2-positive breast cancer, it is estimated that up to 25% of tumors have aberrant PI3K signaling due to mutations in the PIK3CA or PTEN genes leading to constitutive pathway activation (Kalinski 2009, Stemke 2008). In addition, the pathway can be activated by HER2-overexpression itself which likely contributes to tumorigenesis and clinical behavior in patients with HER2-positive breast cancer (Holbro et al 2003).
Moreover, the PI3K pathway seems to be involved in resistance to anti-neoplastic treatments. Preclinical studies have shown that aberrant PI3K signaling can render cell lines resistant to endocrine, HER2-targeted and cytotoxic therapy. For example, PTEN deficiency, PIK3CA mutation and/or activation of other pathways such as IGF1R or members of the growth factor receptor family have been associated with resistance to trastuzumab treatment (Nagata 2004, Berns 2007, Nahta 2005). However, these findings together with the observation that sensitivity may be restored or its effect potentiated by co-administration of PI3K or mTOR inhibitors (Yu 2001, West 2002) provide a rationale for PI3K targeted therapy setting. In fact, recent results from clinical studies with everolimus indeed suggest that the PI3K pathway may be involved in treatment resistance and that targeting the pathway can play a therapeutic role in overcoming resistance to endocrine or HER2-targeted therapy

in breast cancer (Bachelot 2010, Andre 2010).

Study objective

Primair
To determine the MTD and/or RP2D of oral twice daily (BID) BEZ235 in combination with trastuzumab in patients with HER2-positive breast cancer

Secondair
To assess the preliminary activity of the combination
To assess the safety and tolerability of the combination
To describe the pharmacokinetics (PK) of BEZ235 and trastuzumab

Exploratory
To assess pharmacodynamic markers in the context of a BID administration in combination with trastuzumab
To identify molecular profiles relevant to PI3K signaling

Study design

Open-label, dose-finding Phase Ib study followed by an open-label, randomized, active-controlled Phase II study.
Phase Ib will investigate the MTD/RP2D of oral BID dosing of BEZ235 in combination with weekly trastuzumab.

Once the MTD/RP2D has been established, Phase II of the study will start in which patients will be randomized to receive either lapatinib + capecitabine or weekly trastuzumab in combination with BEZ235 BID at the recommended dose for phase II.

Intervention

BEZ235 will be administered twice daily andTrastuzumab infusion will be administered weekly

In Phase two the control group will receive Lapatinib (once daily from D1-D21 of each cycle) and Capecitabine(twice daily from D1-D18 of each cycle)

Study burden and risks

Toxicity of the combination-therapy BEZ 235 and trastuzumab
- Radiation exposure of MUGA (Fase II ook CT/MRI/Botscan)
-Frequent visits and blood sampling
- (optional) tumorbiopsy (Phase II)

An overview of all visits during the procedure are given in Appendix B of the patient information.
The side effects can be found in Appendix C of the patient information.
It is not certain that participation in the study will directly benefit the patient, the data can be useful for the future.
The burden on the patients is as expected for a Phase 1 study.

Contacts

Public
Novartis

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NL
Scientific
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Inclusion criteria applicable to Phase Ib and II:
* Patient is a female * 18 years of age.
* Patient has a histologically and/or cytologically confirmed diagnosis of HER2-positive invasive breast cancer with inoperable locally advanced or metastatic disease

* Patients with controlled or asymptomatic CNS metastases are eligible
* Patient has adequate bone marrow and organ functions, and has recovery from all clinically significant toxicities related to prior anti-neoplastic therapies
- Absolute neutrophil count (ANC) * 1.5 x 109/L
- Platelets * 100 x 109/L
- Hemoglobin (Hgb) * 9.0 g/dL
- INR * 2
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) * 3 x ULN (or * 5.0 x ULN if liver metastases are present)
- Total serum bilirubin * 1.5 x ULN (in patients with known Gilbert Syndrome, a total bilirubin * 3.0 x ULN, with direct bilirubin * 1.5 x ULN)
- Serum creatinine * 1.5 x ULN
- Fasting plasma glucose (FPG) * 140mg/dL [7.8 mmol/L]
- HbA1c * 8%
* Patient has received prior trastuzumab (alone or in combination) but NO more than 3 prior cytotoxic chemotherapy lines
* Prior endocrine and radiotherapy allowed
* Patient has ECOG performance status of 0-2 (Phase Ib) or 0-1 (Phase II)
Additional criteria for Phase II:
* Available tumor tissue (/archival or fresh) for biomarker analysis; known PI3K activation status
* At least one measurable lesion as per RECIST 1.1
* Patient has received prior treatment with a taxane
* Patient has *trastuzumab-resistance disease* defined as:
- Recurrence while on trastuzumab (or T-DM1) or within 12 months since the last infusion in the adjuvant setting
- Progression while on or within 4 weeks since the last infusion of trastuzumab (or T-DM1) in the locally advanced or metastatic setting

Exclusion criteria

Exclusion criteria applicable for Phase Ib and II:
* Previous treatment with PI3K and/or mTOR inhibitors
* Symptomatic/uncontrolled Central Nervous System (CNS) metastases
* Concurrent malignancy or malignancy in the last 3 years prior treatment
* Wide field radiotherapy * 28 days or limited field radiation for palliation * 14 days prior to starting study drug
* Active cardiac disease (e.g. LVEF less than institutional lower limit of normal, QTcF > 480 msec, unstable angina pectoris, ventricular, supraventricular or nodal arrhythmias)
* Inadequately controlled hypertension
* Impairment of gastrointestinal (GI) function or GI disease that may significantly alter the absorption of BEZ235
* Treatment at start of study treatment with drugs with a known risk to induce Torsades de Pointes, moderate and strong inhibitors or inducers of isoenzyme CYP3A4, warfarin and coumadin analogues, LHRH agonists

* Intolerance or contraindications to trastuzumab treatment
* Pregnant or nursing (lactating) woman
Additional exclusion criterion for Phase II:
* Prior treatment with capecitabine and lapatinib
* Intolerance or contraindications to capecitabine and lapatinib
* Previous treatment with HER-2 targeted agents other than trastuzumab or T-DM1
* Peripheral neuropathy * Grade 2

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	25-01-2012
Enrollment:	5
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Tyverb®/Tykerb®
Generic name:	lapatinib
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Xeloda®
Generic name:	capecitabine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Herceptin

Generic name:	trastuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	not yet applicable
Generic name:	not yet applicable

Ethics review

Approved WMO Date:	13-12-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-05-2012
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID

Register	ID
EudraCT	EUCTR2011-003602-25-NL
CCMO	NL38732.042.11