1280.4: A Phase Ib/II Randomized Study of BI 836845 in Combination with Exemestane and Everolimus Versus Exemestane and Everolimus Alone in Women with Locally Advanced or Metastatic Breast Cancer

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A phase Ib / II randomized study of BI 836845 in combination with exemestane and everolimus versus exemestane and everolimus alone in women with locally advanced or metastatic breast cancer.With following objectives:Phase Ib part: To determine the...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Breast neoplasms malignant and unspecified (incl nipple)
Study type	Interventional

Summary

ID

NL-OMON40248

Source
ToetsingOnline

Brief title
1280.4

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, mammacarcinoma

Research involving

Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: Boehringer-Ingelheim

Intervention

Keyword: breast cancer, everolimus, exemestane, hormone receptor positive

Outcome measures

Primary outcome

The primary endpoint of the phase 2 part of the study is progression free survival (PFS), which is defined as the duration of time from the date of C1V1 until the date of the first objective tumor progression or death due to any cause.

Secondary outcome

1. Time to progression (TTP), defined as the duration of time from the date of C1V1 until the date of the first objective tumor progression

2. Objective response (OR), defined as complete response (CR) or partial response (PR)

3. Time to objective response

4. Duration of objective response

5. Clinical benefit (CB), defined as best overall response of complete response (CR) or partial response (PR), or stable disease (SD) *6 months, or Non-CR/Non-PD for *6 months

6. Duration of clinical benefit

Study description

Background summary

Breast cancer is the most common malignancy in women worldwide and is currently the second leading cause of cancer-related death in women. This high mortality rate reflects the limited effectiveness of current therapeutic options, particularly in patients with advanced disease.
Despite recent progress by the introduction of mTOR targeted treatments, hormone-positive advanced or metastatic breast cancer still has a dismal prognosis with a median PFS (Progression Free Survival) of less than one year and almost all patients eventually succumb to their disease.
Early evaluations of ongoing clinical trials of anti-IGF/IGF-1R agents including BI 836845, as monotherapy, and pharmacodynamic studies of BI 836845 in neoplastic cell lines, indicate the possibility of disease stabilization or tumor response in patients with advanced and otherwise incurable cancers.

Study objective

A phase Ib / II randomized study of BI 836845 in combination with exemestane and everolimus versus exemestane and everolimus alone in women with locally advanced or metastatic breast cancer.

With following objectives:
Phase Ib part: To determine the maximum tolerated dose (MTD) and recommended phase II dose of BI 836845 in combination with exemestane and everolimus in women with HR+/HER2- locally advanced or metastatic breast cancer
Phase II part: To evaluate the anti-tumor activity of BI 836845 in combination with exemestane and everolimus versus exemestane and everolimus alone in women with HR+/HER2- locally advanced or metastatic breast cancer

In addition, safety will be assessed.
Also pharmacokinetics (PK), pharmacogenomics and biomarkers will be explored in both Phase I and Phase II part.

Study design

A Phase Ib / II randomized, open-label, multicenter international study in two parts:
* Phase I - single arm, dose escalation with BI 836845 + everolimus + exemestane
* Phase II - two arms, randomized, parallel design, arm 1: everolimus + exemestane arm 2: BI 836845 + everolimus + exemestane
Eligible patients will be randomly assigned in a 1:1 manner in one of the treatment groups. Each arm will enroll approximately 75 patients (total of approximately 150 patients). Randomization will be stratified by visceral

involvement (yes vs. no). Visceral refers to lung, liver, brains, pleural and peritoneal metastases.

Intervention

Phase I part:
Initially a *3+3* dose finding study will be performed to determine the Maximum Tolerated Dose (MTD), Recommended Phase II dose (RP2D) and pharmacokinetics of BI 836845, everolimus and exemestane in women with HR+/HER2- advanced breast cancer. The RP2D will be determined based on MTD in combination with totality of the safety data.
Patients participating in the Phase I part will be concluded for the study participation after the completion of the follow-up visit.

Phase II part:
Once the RP2D is determined, an open-label, two-arm randomized phase II study will commence to further assess the anti-tumor activity of
BI 836845 in combination with exemestane and everolimus in women with HR+/HER2- locally advanced or metastatic breast cancer.
Arm 1 (control arm): Once daily everolimus 10 mg plus once daily exemestane 25 mg orally
Arm 2 (experimental arm): Once daily exemestane 25mg orally, once daily everolimus orally and BI836845 is administered intravenously weekly. The treatment dose of everolimus and BI 836845 will be that of the RP2D from the Phase I part of the study.
Patients will receive continuous daily treatment of everolimus plus exemestane with or without weekly infusions of BI 836845 until progression, intolerable adverse events or other reason necessitating withdrawal. The treatment will be administered as courses of 28 days.

Study burden and risks

Based on the assumption as described in question E2 that the mean duration of the study for the patient will be 10 cycles, the patient will undergo:
- Physical examination: phase 1 + phase 2: 13x
- Weight, blood pressure, pulse and temperature: phase 1: 17x; phase 2: 16x
- ECG: phase 1: 12x; phase 2: 10x
- Safety labs: phase 1: 17x; phase 2: 15x
- blood samples for PK or biomarkers: phase 1: 37x; phase 2, arm 1: 4x; phase 2, arm 2: 19x
- urine sample: phase 1 + phase 2: 2x
- handing in medication diary: only phase 1: 5x
- bone scan and CT chest, abdomen and pelvis and imaging of other suspected sites of disease: phase 1 + phase 2: 5x
- Intravenous administration of BI 836845: only for phase 1 and phase2, arm 2: 40x

Contacts

Public
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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Histologically-confirmed locally advanced or metastatic breast cancer not deemed amenable to curative surgery or curative radiation therapy
- Tumors are positive for estrogen-receptor (ER) and/or progesterone receptor (PgR). Tumors must be negative for HER2 per local lab testing.
- Postmenopausal women
- Objective evidence of recurrence or progression on or after the last systemic therapy prior to the study entry
- Disease refractory to non-steroidal aromatase inhibitors (letrozole and/or anastrozole)
- ECOG<<=2
- Patients must have a measurable lesion according to RECIST version 1.1 or bone lesion only: lytic or mixed (lytic + sclerotic) in the absence of measurable lesions

Exclusion criteria

-Previous treatment with agents targeting on IGF pathway, PI3K signaling pathway, protein kinase B (AKT), or mTOR pathways (sirolimus, temsirolimus, etc.)
-Prior treatment with exemestane
-History of another primary malignancy within 5 years, with the exception of adequately treated in-situ carcinoma of the cervix, uteri, basal or squamous cell carcinoma or non-melanomatous skin cancer

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-08-2014
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	niet van toepassing: zowel specialiteit als generiek kunnen gebruikt worden

Generic name:	exemestane
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nog niet gekend
Generic name:	nog niet gekend

Ethics review

Approved WMO Date:	12-03-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	28-07-2014
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	10-07-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-07-2015
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

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
Other	Clinical trials.gov (NCT02123823); www.clinicaltrialsregister.eu (1280.4)
EudraCT	EUCTR2013-001110-15-NL
CCMO	NL45357.068.14