PI3K pathway analysis in tumor tissue and circulating DNA to obtain further insight in the efficacy of everolimus when combined with exemestane.
A side-study protocol attached to standard treatment with everolimus and exemestane for postmenopausal patients with hormone receptor-positive advanced metastatic breast cancer, who have progressed on anastrozole or letrozole

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In this side-study proposal we plan to gain more insight in tumor characteristics in order to predict which patients will have a high chance of a long progression-free survival. Study objectives: 1. It is proposed to compare progression-free...

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

Summary

ID

NL-OMON46855

Source
ToetsingOnline

Brief title
PI3K pathway in pm breast cancer pts treated with everolimus and exemestane

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
advanced metastatic breast cancer, breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: BOOG study center,Novartis

Intervention

Keyword: Anastrazole, Breast cancer, Letrozole, PI3K pathway

Outcome measures

Primary outcome

Progression

Biomarker study

Secondary outcome

n.v.t.

Study description

Background summary

Study title:
PI3K pathway analysis in tumor tissue and circulating DNA to obtain further insight in the efficacy of everolimus when combined with exemestane
A side-study protocol attached to standard treatment with everolimus and exemestane for postmenopausal patients with hormone receptor-positive advanced metastatic breast cancer, who have progressed on anastrozole or letrozole

Everolimus combined with exemestane has shown to improve progression-free

survival compared to exemestane monotherapy in patients with hormone receptor-positive breast cancer previously treated with non-steroidal aromatase inhibitors. Since January 1st, 2013, everolimus is being reimbursed for this category of patients. For many patients this means, that an interesting treatment possibility has become available. However, some patients do not benefit from everolimus and exemestane, while others have to deal with side-effects requiring adjustment of the dose or even discontinuation of treatment.

Study objective

In this side-study proposal we plan to gain more insight in tumor characteristics in order to predict which patients will have a high chance of a long progression-free survival.
Study objectives:
1. It is proposed to compare progression-free survival on the combination of everolimus and exemestane between patients whose metastatic tumor expresses markers of PI3K pathway activation versus patients whose metastatic tumor does not express PI3K pathway activation (see Attachment 1).
2. It is proposed to carry out immunohistochemistry on activated members of the PI3K pathway in primary tumor tissue of patients treated with everolimus and exemestane and compare the findings with the outcome of treatment and more specifically, with the results from other side-studies (see Attachment 1).
3. It is proposed to associate protein expression/ phosphorylation by proteomics in tumor biopsies to cancer mutations, PI3K pathway activation and progression-free survival on the exemestane and everolimus combination (see Attachment 2).
4. It is proposed to establish the incidence of mutations in PIK3CA and AKT in peripheral blood of advanced breast cancer patients amenable for treatment with everolimus and exemestane and to explore whether the presence of such mutations is associated with outcome to treatment in these patients (see Attachment 3).

Study design

Number of patients and centers:
Since the majority of the side-studies involve the use of new techniques, studies will be mainly explorative in design. For blood sample analysis and analysis of archival tumor tissue at least 175 patients will be required. For tumor tissue biopsies a number of 50 patients is expected to give insight in differences between patients with clinical benefit ant those with early progressive disease; from 30 of these patients a tumor biopsy will be collected upon progressive disease.
- 175 patients for blood samples and archived tumor tissue
- 50 for fresh tumor biopsy,
- 30 for fresh tumor biopsy upon progressive disease
- 30 hospitals in the Netherlands.

Treatment phase:
Patients will be treated with 10 mg daily doses of everolimus (either 2 x 5 mg or 1 x 10 mg tablets) in combination with exemestane (25 mg daily tablets). Dose adjustment (reduction, interruption) according to safety findings will be allowed.
Treatment will continue until one of the following conditions apply and whichever comes first: tumor progression, unacceptable toxicity according to investigator*s judgment, death, discontinuation from the study for any other reason. Further treatment after progression will be at the investigator*s discretion.
Physicians will collect data on demographics, previous treatments, efficacy of everolimus and exemestane as well as on toxic effects of this combination according to GCP in the patient*s file.

Study burden and risks

This study will not provide any direct benefit for the patients participating in this study. The burden for the patients is low and risks of participating are negligible to low.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Adult women (* 18 years of age) with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy.
2. Histological or cytological confirmation of estrogen-receptor positive (ER+) breast cancer.
3. Postmenopausal women.
4. Disease refractory to non steroidal aromatase inhibitors (NSAI).

Exclusion criteria

1. HER2-overexpressing patients by local laboratory testing (IHC 3+ staining or in situ hybridization positive).
2. Previous treatment with mTOR inhibitors.
3. Radiotherapy within four weeks prior to enrollment except in case of localized radiotherapy for analgesic purpose or for lytic lesions at risk of fracture which can then be completed within two weeks prior to enrollment. Patients must have recovered from radiotherapy toxicities prior to enrollment.
4. Currently receiving hormone replacement therapy, unless discontinued prior to enrollment.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-03-2014

Enrollment:	175
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:	Aromasin
Generic name:	Exemestane
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	07-11-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	27-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	05-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-03-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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
EudraCT	EUCTR2013-004120-11-NL
ClinicalTrials.gov	NCT02109913
CCMO	NL46195.029.13