A Randomized Double-Blind, Placebo-Controlled Study of Everolimus in Combination with Exemestane in the Treatment of Postmenopausal Women with Estrogen Receptor Positive Locally Advanced or Metastatic Breast Cancer who are refractory to Letrozole or Anastrozole.

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To compare the combination treatment of everolimus and exemestane to exemestane alone with respect to progression-free survival in postmenopausal women with estrogen receptor positive breast cancer that is refractory to non-steroidal aromatase...

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

Summary

ID

NL-OMON35415

Source
ToetsingOnline

Brief title
Phase III study with RAD001 in ABC or MBC

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast carcinoma / breast cancer

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Advanced/Metastatic, Breast Cancer, Everolimus, Exemestane

Outcome measures

Primary outcome

The primary endpoint in this study is progression-free survival (PFS), defined as the time from date of randomization to the date of first documented progression or death due to any cause. If a patient has not had an event, PFS will be censored at the date of last adequate tumor assessment.

Secondary outcome

- To compare the two treatment arms with respect to Overall Survival (OS).

- To evaluate the two treatment arms with respect to

o Overall response rate (ORR)

o Time to deterioration of ECOG performance status

o Safety

o Changes in Quality of Life (QoL) scores over time

o Clinical benefit rate (CBR)

- To summarize time to response and duration of response in the two treatment arms.

Study description

Background summary

Approximately 70% of all invasive breast cancers are positive for ER and/or PgR expressions at the time of diagnosis. Deprivation of estrogenic signaling with the anti-estrogen tamoxifen has been the main form of hormonal treatment for over 30 years. While therapies which interfere with ER functions such as tamoxifen have significantly contributed to mortality reduction in advanced breast cancer patients, at best 50-60% of ER-positive patients respond to anti-estrogen therapy. Consequently, a number of aromatase inhibitors (AIs) that reduce peripheral estrogen synthesis have been developed for the treatment of advanced breast cancer (ABC). The third generation AIs can be broadly classified into two groups: non-steroidal aromatase inhibitors (NSAI), mainly letrozole (Femara®) and anastrozole (Arimidex®) and the steroidal aromatase-inactivator, exemestane (Aromasin®).

There are currently no treatments specifically approved for postmenopausal women with ER positive breast cancer after recurrence or progression on a non steroidal aromatase inhibitor (letrozole or anastrozole). To date, treatment of these patients remains an area of unmet medical need.

Activation of the mTOR pathway is a key adaptive change driving endocrine resistance. Research into the mechanisms of resistance has shown that various signal transduction pathways are activated to escape the effect of endocrine therapy. Everolimus is a derivative of rapamycin that acts as a signal transduction inhibitor. An important aspect of the anti-tumor effect of everolimus is its potential to act both on tumor cells directly (to inhibit growth) and indirectly (by inhibiting angiogenesis and displaying anti-vascular properties). Everolimus and letrozole synergistically inhibit proliferation in BC cells. mTOR inhibition provides additional efficacy to long term estrogen deprivation and has an acceptable level of tolerability in the neoadjuvant setting.

Study objective

To compare the combination treatment of everolimus and exemestane to exemestane alone with respect to progression-free survival in postmenopausal women with estrogen receptor positive breast cancer that is refractory to non-steroidal aromatase inhibitors.

Study design

This is a multicenter, double-blind, randomized, placebo-controlled, international phase III study.

Patients will be randomized in 2:1 ratio to receive either everolimus or matching placebo in a blinded manner in addition to open label exemestane (25 mg daily tablets). Considering the safety of exemestane is already well established, the 2:1 randomization ratio will allow collection of more data from the experimental arm to better evaluate the safety of the everolimus-exemestane combination.

Study treatment will continue until progression, intolerable toxicity or consent withdrawal. Further treatment after progression will be at the investigator*s discretion. Subjects on placebo arm will not be allowed to cross over to study supplied everolimus at the time progression, as everolimus remains an investigational drug for this patient.

Intervention

Patients will be randomized in 2:1 ratio to receive either everolimus (2 tablets × 5 mg daily) or matching placebo in a blinded manner, in addition to open label exemestane (25 mg daily tablets).

Study burden and risks

- Every potential side effect of everolimus and/or exemestane.
- Radiation exposure of X-rays and/or CT scans.
- Obtaining blood samples may cause some discomfort, bruising, bleeding from the site of sampling, formation of a blood clot, and, in rare cases, infection.

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

- Adult women (* 18 years of age) with metastatic or locally advanced breast cancer not amenable to curative treatment by surgery or radiotherapy.
- Histological or cytological confirmation of estrogen-receptor positive (ER+) breast cancer.
- Postmenopausal women.
- Disease refractory to non steroidal aromatase inhibitors (NSAI).
- Radiological or clinical evidence of recurrence or progression on last systemic therapy prior to randomization.
- ECOG Performance Status * 2.
-Patients must have:
1. At least one lesion that can be accurately measured in at least one dimension * 20 mm with conventional imaging techniques or * 10 mm with spiral CT or MRI or
2. bone lesions: lytic or mixed (lytic + sclerotic) in the absence of measurable disease.

Exclusion criteria

- HER2-overexpressing patients by local laboratory testing (IHC 3+ staining or in situ hybridization positive).
- Patients with only non-measurable lesions other than bone metastasis (e.g. pleural effusion, ascites etc.).
- Patients who received more than one chemotherapy regimen for ABC.
- Previous treatment with exemestane or mTOR inhibitors.
- Known hypersensitivity to mTOR inhibitors, e.g. sirolimus (rapamycin).
- Another malignancy within 5 years prior to randomization.
- Radiotherapy within four weeks prior to randomization.
- Currently receiving hormone replacement therapy, unless discontinued prior to randomization.
- Symptomatic brain or other CNS metastases.

- Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use at the time of study entry.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-07-2009
Enrollment:	35
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Aromasin
Generic name:	Exemestane
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	Everolimus

Ethics review

Approved WMO

Date:	25-05-2009
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	30-07-2009
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	12-04-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	17-05-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	27-05-2010
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	25-02-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	19-05-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	30-05-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO	

Date:	10-06-2011
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	12-01-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	14-02-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	16-01-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	22-08-2014
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	22-09-2014
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

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	EUCTR2008-008698-69-NL
CCMO	NL28031.094.09