Onderzoek naar kenmerken in tumorweefsel en bloed, die informatie kunnen geven over de werkzaamheid van everolimus in combinatie met exemestaan

No registrations found.

Ethical review	Positive opinion
Status	Recruiting
Health condition type	-
Study type	Interventional

Summary

ID

NL-OMON21846

Source
NTR

Health condition

borstkanker, mammacarcinoom, gemetastaseerd, everolimus, exemestaan, biomarker.
breast cancer, metastatic, everolimus, exemestane, biomarker.

Sponsors and support

Primary sponsor: VU University Medical Center
Source(s) of monetary or material Support: Novartis

Intervention

Outcome measures

Primary outcome

Biomarker Evaluation from Primary Tumor Tissue, New Tumor Biopsies and Blood Samples.

Progression-free survival.

Secondary outcome

Number of Participants with Adverse Events as a Measure of Safety and Tolerability

Study description

Background summary

Although endocrine therapy has changed survival of patients with advanced hormone receptor-positive breast cancer, many tumors exhibit de novo resistance and the remainder acquire resistance during treatment. Studies in vitro have shown that growth factor signaling pathways, particularly the phosphatidylinositol 3-kinase (PI3K) route, can mediate resistance to endocrine therapy. One of the PI3K pathway-targeted drugs is the TORC1 inhibitor everolimus. Everolimus combined with the aromatase inhibitor exemestane improved progression-free survival in patients with hormone receptor-positive breast cancer as compared to exemestane alone. However, some patients did not benefit from the combination asking for better selection of patients for this new treatment approach. The aim of this study is to determine tumor characteristics that predict efficacy for everolimus and exemestane .

Patients will be treated with everolimus and exemestane. In the BOOG network, 30 hospitals will participate. For blood samples and archival tumor tissue collection 175 patients are required. For fresh tumor biopsy at the start of treatment 50 patients are required and from 30 of these, tumor biopsy will also be collected upon progressive disease. Case Record Forms will be designed and data shall be collected from each patient. Reasons for dose reduction and discontinuation will be recorded. Progression-free survival will be calculated. In patients without evidence of progression but stopped treatment 1) the time-to-treatment switch or 2) death, will serve as primary endpoint. Immunohistochemistry on tumor tissue will be carried out focused on PI3K pathway-associated proteins. Proteomics and ChIP/mRNA-seq experiments will be performed in tumor biopsies. Circulating DNA will be assessed for mutations in PI3K and AKT. Laboratory findings will be linked with data on treatment efficacy.

In conclusion, this project will gain more insight in tumor characteristics to predict which patients will benefit from treatment with everolimus and exemestane. It may also point towards other possible targets for treatment with future PI3K pathway inhibitors.

Study objective

Gain more insight in tumor characteristics in order to predict which patients will have a high chance of a long progression-free survival.

Study design

Before start therapy until progression (expected average until progression: 11 months)

Intervention

Patients will be treated according to standard care, 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.

Blood samples and archived tumor tissue will be collected at baseline.

At baseline, optional fresh tumor biopsies is asked, and also upon progressive disease.

Contacts

Public
VUMC
Dinja Kruger
Amsterdam
The Netherlands
Scientific
VUMC
Dinja Kruger
Amsterdam
The Netherlands

Eligibility criteria

Inclusion criteria

Patients eligible for inclusion in this side-study have to meet all of the following 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. Postmenopausal status is defined either by:

- Age > 55 years and one year or more of amenorrhea

- Age < 55 years and one year or more of amenorrhea, with an estradiol assay < 40 pg/ml

- Surgical menopause with bilateral oophorectomy

4. Disease refractory to NSAI, defined as:

- a. Recurrence while on or within 12 months of end of adjuvant treatment with letrozole or anastrozole, or

b. Progression while on or within one month of end of letrozole or anastrozole treatment for advanced BC (locally advanced or metastatic)

- Note: Letrozole or anastrozole do not have to be the last treatment prior to enrollment. Other prior anticancer therapy, e.g. tamoxifen, fulvestrant are allowed. Patients must have recovered to grade 1 or better from any adverse events (except alopecia) related to previous therapy prior to enrollment.

- Radiological or clinical evidence of recurrence or progression on last systemic therapy prior to enrollment.

- Note: There are no restrictions as to the last systemic therapy prior to enrollment.

5. Adequate bone marrow and coagulation function as shown by:

- Absolute neutrophil count (ANC) > 1.5 ¡Á109/L

- Platelets > 100 ¡Á109/L

- Hemoglobin (Hgb) > 5.6 mmol/L

- INR ¡Ü 2.0

6. Adequate liver function as shown by:

- Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ¡Ü 2.5 ULN (or ¡Ü 5 if hepatic metastases are present)

- Total serum bilirubin ¡Ü 1.5 ¡Á ULN (¡Ü 3 ¡Á ULN for patients known to have Gilbert Syndrome)

7. Adequate renal function as shown by:

- Serum creatinine ¡Ü 1.5 ¡Á ULN

8. Fasting serum cholesterol ¡Ü 7.75 mmol/L and fasting triglycerides ¡Ü 2.5 ¡Á ULN. In case one or both of these thresholds are exceeded, the patient can only be included after initiation of statin therapy or other lipid lowering drugs (eg fibrates), and when the above mentioned

values have been achieved

9. Written informed consent obtained before any screening procedure and according to local guidelines.

Exclusion criteria

Patients eligible for this study must not meet any of the following criteria:

1. HER2-overexpressing patients by local laboratory testing (IHC 3+ staining or in situ hybridization positive).

2. Previous treatment with exemestane or mTOR inhibitors. Except for the treatment with exemestane in the adjuvant setting providing patient remained disease-free for at least one year following completion.

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.

5. Patients receiving concomitant immunosuppressive agents or chronic corticosteroids use, at the time of study entry except in cases outlined below:

6. Topical applications (e.g. rash), inhaled sprays (e.g. obstructive airways diseases), eye drops or local injections (e.g. intra-articular) are allowed.

7. Patients on stable low dose of corticosteroids for at least two weeks before enrollment are allowed in case of treatment of brain metastases.

8. Bilateral diffuse lymphangitic carcinomatosis or metastasis of the lung as the only manifestation of disease (>50% of lung involvement), evidence of metastases estimated as more than a third of the liver as defined by sonogram and/or CT scan.

9. Patients with a known history of HIV seropositivity.

10. Active, bleeding diathesis, or on oral anti-vitamin K medication (except low dose warfarin and acetylsalicylic acid or equivalent, as long as the INR is ¡Ü 2.0)

11. Any severe and / or uncontrolled medical conditions such as:

- Unstable angina pectoris, symptomatic congestive heart failure, myocardial infarction ¡Ü6 months prior to enrollment, serious uncontrolled cardiac arrhythmia

- Uncontrolled diabetes as defined by fasting serum glucose > 1.5 ¡Á ULN

- Acute and chronic, active infectious disorders (except for hepatitis B and C positive patients) and nonmalignant medical illnesses that are uncontrolled or whose control may be jeopardized by the complications of this study therapy

- Impairment of gastrointestinal function or gastrointestinal disease that may significantly alter the absorption of study drugs (e.g., ulcerative disease, uncontrolled nausea, vomiting, diarrhea, malabsorption syndrome)

- Significant symptomatic deterioration of lung function. If clinically indicated, pulmonary function tests including measures of predicted lung volumes, DLco, O2 saturation at rest on room air should be considered to exclude restrictive pulmonary disease, pneumonitis or pulmonary infiltrates.

12. Patients who test positive for hepatitis B or C (patients who test negative for HBV-DNA, HBsAg, and HBcAb, but positive for HBsAb with prior history of vaccination against Hepatitis B will be eligible ¨C see also 1.4)

13. Patients being treated with drugs recognized as being strong inhibitors or inducers of the isoenzyme CYP3A (rifabutin, rifampicin, clarithromycin, ketoconazole, itroconazole, voriconazole, ritinavir, telithromycin) within the last 5 days prior to enrollment

14. History of non-compliance to medical regimens

15. Patients unwilling to or unable to comply with the protocol

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Non controlled trial
Masking:	Open (masking not used)
Control:	N/A , unknown

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	20-03-2014
Enrollment:	175
Type:	Anticipated

Ethics review

Positive opinion Date:	01-04-2014
Application type:	First submission

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
NTR-new	NL4447
NTR-old	NTR4570
Other	BOOG 2013-06, ClinicalTrials.gov Identifier: : METC VUmc 2013.406, EUDRACT: 2013-004120-11

Study results