A single arm multicenter biomarker study determining the response to taxane-based chemotherapy in metastatic breast cancer (MBC) patients with ESR1 mutations in cell-free DNA: TAX-ESR1 study.

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

Summary

ID

NL-OMON46354

Source
ToetsingOnline

Brief title
TAX-ESR1 study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Metastasis of breast cancer

Research involving

Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam
Source(s) of monetary or material Support: KWF

Intervention

Keyword: ESR1 mutation, Metastatic breast cancer, Taxane-based chemotherapy

Outcome measures

Primary outcome

The primary endpoint for this study will be the progression free survival rate at 6 months (PFS6mnths) in ESR1 mutated MBC patients treated with taxane-based chemotherapy.

Secondary outcome

Outcome to taxane-based chemotherapy in ESR1 mutated and wild-type patients measured as progression free-rate at 6 months, progression free survival and overall survival.

The relation between serial measurement of ESR1 mutations and clinical follow-up data (i.e. survival and efficacy).

The relation between different activating ESR1 mutations (e.g. D538G and Y537S) and treatment outcome measured as progression free- and overall survival.

The assessment of baseline and progression ESR1 mutational status, in order to learn whether ESR1 mutations can be lost during treatment.

Study description

Background summary

Endocrine treatment is the mainstay of treatment for ER- positive metastatic breast cancer (MBC). Unfortunately, 40% of patients have no clinical benefit from first-line endocrine therapy due to intrinsic resistance, whereas the remainder of patients initially responding will eventually develop resistance during therapy (1). Importantly, once the tumor develops resistance to endocrine therapy, the tumor becomes more aggressive, leading to a poor prognosis (2). Recently, mutations in the gene encoding ERα, ESR1, have attracted particular interest as a mechanism for endocrine resistance in MBC. Functional studies have shown that somatic mutations in the ligand-binding domain (LBD) of ESR1 result in constitutive activity of ERα in absence of its ligand estrogen (3). This indicates a mechanism that directly leads to endocrine resistance. These functional studies have been supported by clinical data of the SoFEA and BOLERO-2 trials. Both studies showed an impaired progression-free survival (PFS) in ESR1 mutated patients versus wild-type patients treated with an aromatase inhibitor (AI) (4,5). In addition, in the BOLERO-2 study, patients with an ESR1 mutation had overall an impaired overall survival (OS) compared to wild-type patients, indicating a more aggressive disease biology.
The impaired effectiveness of AIs in the ESR1 mutated patients raises the question from which therapy these patients still could benefit and which is the most effective. Therefore, we present here a biomarker study to investigate whether ESR1 mutated patients could still benefit from taxane-based chemotherapy.

Study objective

The primary objective of this study is to assess the outcome of taxane- based chemotherapy in ER-positive MBC HER2-negative patients with progression after receiving endocrine therapy (with at least an AI) who have an ESR1 mutation measured in circulating tumor DNA (ctDNA). Secondary objectives include whether serial measurement of ESR1 mutations can predict survival and/or efficacy of taxane-based chemotherapy; investigate whether different activating ESR1 mutations result in differences in treatment efficacy and study if chemotherapy can result in loss of ESR1 mutations.

Study design

This is a multicenter, prospective, biomarker study. From all patients, blood will repeatedly be drawn at baseline and during treatment at 2-3 weeks, after 6 weeks, after 3 months, after completion of the chemotherapy, at 6 months and at

the time of disease progression.

Study burden and risks

Of all patients 2x10 mL will be drawn at baseline, and six additional time points during treatment and at disease progression. The blood draws will be taken when patients need to undergo blood draws for standard care as much as possible. The risk of longitudinal blood collections by venipuncture is negligible. Treatment response and disease progression will be assessed according to current clinical guidelines. There will be no benefits for the patients included in this study.
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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. Female metastatic breast cancer patients with ER-positive, HER2- negative primary tumors;
2. Previous treatment with at least an aromatase inhibitor either in adjuvant and/or metastatic setting;
3. Failure to previous treatment with at least one type of aromatase inhibitor (non-steroidal/steroidal) for MBC;
4. Considered fit enough to receive taxane-based chemotherapy by the treating physician; either as a first line chemotherapy for metastatic breast cancer or as second line treatment if the time between completion of first line chemotherapy for metastatic breast cancer and inclusion is more than three years.
5. Intention to start with either paclitaxel and docetaxel;
6. Patient with measurable or clinically evaluable (bone only) disease on recent standard work-up for MBC;
7. CT chest and abdomen must not be older than 42 days on the day of the anticipated treatment start;
8. Age >=18 years old;
9. WHO performance status 0-2;
10. Signed written informed consent;

Exclusion criteria

1. Previous chemotherapy for metastatic disease, completed within three years before inclusion;
2. Patients with locally advanced disease, primary not amendable for resection or radiation therapy with curative intent;
3. (neo)adjuvant chemotherapy within 6 months prior to treatment start;
4. Anti-hormonal treatment for breast cancer within two weeks prior to treatment start;
5. Symptomatic CNS metastasis (the presence of at least one key symptom in combination with radiologic evidence (positive contrast-enhanced CT or MRI of the brain)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	07-12-2017
Enrollment:	175
Type:	Actual

Ethics review

Approved WMO Date:	23-11-2017
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-06-2018
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-01-2019
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-02-2021
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 25511
Source: NTR
Title:

In other registers

Register	ID
CCMO	NL62417.078.17