Can molecular imaging predict outcome to firstline endocrine treatment ± CDK 4/6 inhibition in advanced ER+ breast cancer?

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

Summary

ID

NL-OMON53479

Source
ToetsingOnline

Brief title
SONImage

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Mammary carcinoma - Breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: KWF Kankerbestrijding,Pfizer

Intervention

Keyword: Breast cancer, CDK 4/6 inhibitor, Endocrine therapy, Molecular imaging

Outcome measures

Primary outcome

The study parameters and endpoints are entirely the same as in the original SONImage side study.

The primary study endpoint (1) is PFS (according to RECIST 1.1 criteria, Appendix 1) after first line treatment (PFS1).

Secondary outcome

Secondary study endpoints are:

- Interaction between baseline FES-PET heterogeneity score, treatment allocation, and PFS1 (according to RECIST 1.1 criteria) (2)

- Correlation between response measurements of individual lesions to baseline FES-PET heterogeneity score and detailed FES and FDG imaging features (3)

- Development of a multivariable model to predict individual PFS benefit to first-line aromatase inhibitor ± CDK 4/6 inhibition, based on detailed FES/FDG image features and standard clinicopathological information (4)

- Validation of this prediction model (5)

- To determine circulating tumor DNA (ctDNA) in plasma, to investigate the prognostic and possibly predictive values of these measures (6)

- Percentage change in FES-PET heterogeneity score after 1st line endocrine treatment ± CDK 4/6 inhibition visualized with FES-PET and FDG-PET imaging at PFS1 (7).

Study parameters: the following candidate predictors will be evaluated for their potential association with the primary and secondary endpoints:

1. Baseline FES-PET heterogeneity score per patient measured in categories (0%-, 1-99%- and 100% FES-positive disease) and as a continuous variable.

2. Detailed baseline FES- and FDG-PET features and other radiomics features of within-patient and within-lesion heterogeneity patterns, including features of disease indolence and aggressiveness.

3. Standard baseline clinicopathological predictors and treatment allocation.

This analysis will allow development of a multivariable prediction model to predict individual PFS benefit to first-line aromatase inhibitor ± CDK 4/6 inhibition which will then be validated in other MBC patient cohorts with similar procedures at baseline

4. FES-PET heterogeneity score per patient measured in the aforementioned categories at progression

Study description

Background summary

Currently, the estrogen receptor (ER) is the only reliable predictive biomarker for responsiveness to endocrine therapy in combination with cyclin-dependent kinase (CDK) 4/6-inhibitors in patients with metastatic breast cancer (MBC). The ER status of a single biopsy alone, however, might not be representative of the ER status of all cancerous lesions in one patient. One of the factors at play here is presumably disease heterogeneity. The 18F-fluoroestradiol (FES)-PET scan visualizes ER expression in lesions throughout the body, providing insight in whole body ER heterogeneity (1,2,3). Previously, we performed baseline FES-PET and 18F-fluorodeoxyglucose (FDG)-PET scans in 30 patients with ER+ advanced breast cancer, prior to start of the aromatase inhibitor and the CDK 4/6 inhibitor palbociclib. In this study, we used the term FES-PET heterogeneity score, which refers to the percentage of ER+

metastases in the body (seen on FES-PET) compared to the total number of metastases (seen on FDG-PET); therefore, homogenous ER+ disease yields highest score. Using categories based on this FES-PET heterogeneity score, it was found that median time to progression (TTP) was 73 weeks for patients who had FES uptake (SUVmax >=2) in all FDG positive metastases (100% FES-positivity), 27 weeks with a heterogeneous disease (1-99% FES-positivity), and only 15 weeks without FES-positive disease (0% FES-positivity) (3).

Study objective

Based on the data as described above, we hypothesize that the FES-PET heterogeneity score can predict progression free survival (PFS) in individual patients prior to start of 1st line endocrine treatment and CDK 4/6 inhibition in ER+ advanced breast cancer. In SONImage, we want to investigate this hypothesis further. Ultimately the goal is to develop a molecular imaging based multivariable model, to predict individual PFS benefit to 1st line aromatase inhibition (aromatase inhibitor) ± CDK 4/6 inhibition. This would allow patients and providers to weigh individual benefits and (long-term) burden for optimized treatment decisions. In addition, we hypothesize that first line endocrine treatment ± CDK 4/6 inhibitor treatment itself can induce (further) heterogeneity of whole-body ER expression which can affect response to subsequent second line (fulvestrant ± CDK 4/6 inhibition) treatment in ER+ MBC.

Study design

This is an extension to the SONImage study, an imaging biomarker side study to the Dutch SONIA trial. In the SONIA trial, patients with ER+ advanced breast cancer were randomized to endocrine treatment combined with CDK 4/6 inhibition either in first or second line. Due to the COVID-19 pandemic disproportionally affecting inclusion in SONImage compared to SONIA, the inclusions goals of SONImage could not be met before the closure of the SONIA trial. Instead of 100 patients, 53 patients have been entered in SONImage: 31 were randomized to endocrine therapy plus a CDK 4/6 inhibitor (strategy A SONIA) and 22 patients to standard first-line endocrine therapy (strategy B SONIA). To meet the primary endpoint of SONImage after the completion of SONIA, SONImage will be extended as an independent study to complete inclusion of 50 evaluable patients in the CDK 4/6 inhibitor treatment arm. For the endocrine treatment alone arm, the total number of 50 evaluable patients will be complemented by random sampling from the completed IMPACT MBC trial (NCT01957332, Schröder PI), in which similar patients received exactly the same imaging modalities prior to start of 1st line endocrine treatment (without CDK 4/6 inhibition) for ER+ advanced breast cancer.

Study burden and risks

The FES-PET scan performed at baseline and at PFS1, plus low-dose CT scan, will

induce an extra radiation burden of about 6.1 mSv each (210 MBq injected per scan for an average patient of 70 kilogram body weight). This additional radiation burden is justifiable in this category of adult patients with advanced cancer according to the International Commission on Radiological Protection (ICRP) guidelines. One venous blood sample (6 mL) will be drawn during the FES-PET procedure for sex hormone binding globulin (SHBG) measurement and, in case the patient gives consent, three venous blood samples (30mL) at baseline and PFS1 for ctDNA analysis. The time between FES-PET and standard FDG-PET (in no specific order) should be at least 24 h to allow for sufficient decay of the radiotracer. Patients and physicians will be blinded for the FES-PET results but not for FDG-PET. The results generated from this imaging side study will have no clinical implications for the individual study participants.

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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 proven diagnosis of adenocarcinoma of the breast with locoregional recurrent or metastatic disease not amenable to resection or radiation therapy with curative intent and for whom chemotherapy is not clinically indicated.
2. Previously untreated with any systemic anti-cancer therapy for metastatic HR+ disease, with the exception of recently started (within 14 days of start treatment) endocrine therapy.
Special considerations:
a. Previous systemic treatment for locoregional recurrent disease is not an exclusion criterion, provided that the intent was curative at the time of systemic therapy.
b. In case of previous systemic treatment for oligometastatic disease, patients are not eligible for SONImage
3. Documentation of histologically confirmed diagnosis of ER expression >10% breast cancer
based on local results (on the primary tumor or on a metastatic lesion).
4. Patients that are planned to start with an aromatase inhibitor + CDK 4/6 inhibitors within 28
days of signing informed consent.
5. Women who are not post-menopausal must receive ovarian ablation or suppression with
administration of LHRH agonist. Postmenopausal status is defined as:
a. prior bilateral surgical oophorectomy, or
b. for patients >=60 years: spontaneous cessation of regular menses for at least 12 consecutive months without OAC;
c. for patients <60 years: spontaneous cessation of regular menses for at least 12 consecutive months without OAC ánd estradiol and FSH levels that meet postmenopausal values according to local reference values at screening
6. Able to give written informed consent and to comply with the SONImage protocol.

Exclusion criteria

1. Contra-indication for aromatase inhibitors.
2. Contra-indication for PET imaging.
3. Use of ER ligands (i.e., tamoxifen or fulvestrant) <= 5 weeks before FES-PET imaging.
4. Use of CDK4/6 inhibitor before FES-PET or FDG-PET imaging.
5. Use of aromatase inhibitors > 2 weeks before FES-PET or FDG- PET imaging.
Prior to FDG/FES-PET CT imaging performed after PFS1 before start of second line fulvestrant ± CDK 4/6 inhibition, the same in- and exclusion criteria apply. In addition:

1. Patients must be included in SONImage at start of first line therapy.
2. Patients are excluded when there is a contra-indication for fulvestrant
3. Patients are excluded when fulvestrant is used > 2 weeks before FDG-PET imaging
4. Patients are excluded when fulvestrant is used before FES-PET imaging

Study design

Design

Study phase:	3
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	23-03-2023
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO

Date:	01-02-2023
Application type:	First submission
Review commission:	METC NedMec

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
ClinicalTrials.gov	NCT04125277
CCMO	NL82504.041.22