FUnctional selection of advanced breast cancer patients for Talazoparib treatment Using the REpair Capacity (RECAP) test: The FUTURE trial

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This study has been transitioned to CTIS with ID 2024-518036-36-01 check the CTIS register for the current data. To prove that the RECAP test has the potential of selecting patients who are sensitive to treatment with the PARP inhibitor talazoparib...

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

Summary

ID

NL-OMON54538

Source
ToetsingOnline

Brief title
the FUTURE trial

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast carcinoma, Breastcancer

Research involving
Human

Sponsors and support

Primary sponsor: Erasmus MC, Universitair Medisch Centrum Rotterdam

Source(s) of monetary or material Support: Pfizer

Intervention

Keyword: Breast cancer, Homologous recombination deficiency, PARP inhibitor, Predictive test

Outcome measures

Primary outcome

The aim of the current study is to assess the predictive potential of the RECAP test for in vivo response to talazoparib treatment by investigating the percentage of patients with HRD breast tumors with PFS on talazoparib monotherapy of 4 months or longer. The main endpoint is thus the proportion of patients with PFS at 4 months (PFS4).

Secondary outcome

Secondary endpoints are overall response rate (ORR), overall survival (OS) among patients with HRD tumors treated with talazoparib. The negative predictive value will be determined within the HRP group.

Study description

Background summary

Optimal patient selection for poly (adenosine diphosphate [ADP]-ribose) polymerase (PARP) inhibitors (PARPi) and double strand break (DSB) inducing chemotherapy is of great clinical importance. Although evidence is emerging that the use of these therapies could be extended beyond germline BRCA1/2 mutated cancers, a gold standard test for predicting response to treatments targeting homologous recombination(HR) is not yet available. Recently, we have developed the REpair CAPacity (RECAP) test, a functional assay exploiting RAD51 (a DSB repair protein) foci formation after ex vivo irradiation of fresh breast cancer tissue. This allows testing of the HR status on a real-time basis.
Within a cohort of 148 primary breast carcinomas (BrC), we found that 16% of the tumors (n=24) were HR deficient (HRD) (Meijer et al, submitted/ under

review). Besides on primary BrC, we have also shown that execution of the functional RECAP test on small core needle biopsies from metastatic BrC lesions is achievable and produces robust and interpretable results for most patients (93%) (unpublished data). Within an unselected cohort of metastatic BrCs lesions, 32% (13 out of 41 biopsies) were HRD according to the RECAP test. Molecular characterization of HRD tumors revealed BRCA1/2 germline (gBRCA) mutations, somatic mutations, deletions and promotor methylation. Interestingly, 31% of primary HRD and 46% of metastatic HRD BrCs lesions could not be explained by any form of BRCA deficiency. Among non-BRCA HRD tumors, one tumor harbored a PALB2 mutation. Thus, based on the HR phenotype rather than BRCA germline status, more patients can be identified who are likely to benefit from PARPi treatment. Furthermore, the RECAP test can also detect reversion of the HRD phenotype in BRCA deficient tumors, that have been treated with various DNA damaging chemotherapies that may have induced resistance, and thereby prevent unnecessary treatment. Consequently, it is of the utmost importance to determine the predictive value of the RECAP test for the in vivo response to PARPi. Talazoparib is one of the most promising PARPi, given its significant potency and superior PARP-trapping properties compared to other PARPi.

Study objective

This study has been transitioned to CTIS with ID 2024-518036-36-01 check the CTIS register for the current data.

To prove that the RECAP test has the potential of selecting patients who are sensitive to treatment with the PARP inhibitor talazoparib as measured by the PFS rate at 4 months.

Study design

This is a single arm, prospective multicenter study among patients with advanced breast cancer with proven HRD phenotype who will be treated with talazoparib, a strong PARP inhibitor. After signing informed consent, metastatic breast cancer patients will undergo an ultrasound (or CT-) guided biopsy in order to obtain at least two biopsies from a metastatic lesion to determine the HR status by the RECAP test and a blood withdrawal for determination of ctDNA isolation. HRP patients will not receive talazoparib but will be treated according to physicians choice. Therapy response will be part of the follow-up. About 30% of screened patients will have an HRD tumor and thus will be eligible to start talazoparib monotherapy until PD or unacceptable side effects. The primary endpoint is PFS at four months. Additional endpoints will be among others overall response rate and overall survival. Upon progression, patients wil be kindly asked for consent to perform another biopsy (optional) and blood withdrawal in order to prove reversibility of the RECAP test outcome (from HRD to HRP) and explore potential mechanisms of resistance

(ctDNA changes). For example, BRCA reversion mutations have been associated with Talazorparib resistance and can be identified in ctDNA.

Intervention

Talazoparib single agent, daily 1 mg orally

Study burden and risks

Burden for the patient will be minimal because only easily approachable metastatic lesions will be offered for a biopsy. Bone and lung metastasis will be excluded from this study to avoid risks and side effects. Expected but confined effects will be mild pain and in the worst case a(n extended) bleeding. Furthermore, talazoparib is an oral drug taken on a daily-base which may lead to side effects. From previous studies, it is known that these are overall mild and seldom result in premature end of study participation

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Inclusion criteria

• Age >=18 years
• WHO performance status 0-2
• Locally advanced breast cancer without curative intent or metastatic breast cancer
* The breast cancer must be either
o high grade (Bloom & Richardson grade 3) ER positive (>10%) and HER2 negative primary breast cancer, or
o triple negative (ER<10%, PR<10% and HER2 negative), or
o any Bloom & Richardson grading and receptor status and also
* at least one metastatic lesion must have a proven HRD phenotype based on a RECAP test not treated with anticancer therapy thereafter or
* the patient must have a proven germline or somatic BRCA1 and/or BRCA2 mutation
• The site of the metastatic lesion (or primary tumor in case it is still in situ) should be easily amendable for biopsy. NB lung metastases (high risk of hemato/pneumo-thorax) and bone metastases (not suitable for RECAP test because calcifications interfere with experimental procedures) are excluded. The local guidelines will be used for stopping and restarting of anticoagulation.
Bilirubin <1.5 ULN (except elevated bilirubin due to Gilbert*s disease or a similar syndrome involving slow conjugation of bilirubin) and both AST and ALT <5x ULN in case a liver biopsy is planned.
• The tumor must be HRD, defined as HRD identified by the RECAP test determined just before the start of potential Talazoparib treatment within this study or just (also in case a proven germline BRCA1/2 mutation is present).
• Maximum of four prior lines of chemotherapy for advanced disease; Patients who received platinum compounds are eligible if they have had at least a progression free interval of four months.
• Measureable or evaluable disease according to RECIST 1.1 criteria (appendix 2)
• Life expectancy >= 3 months
• Hemoglobin >= 10 g/dL (6,2 mmol/L) and ANC of >= 1.5 x 109 /L
• Platelets >100 x 10e9/L
• Hepatic function as defined by total serum bilirubin <= 1. 5 x ULN (except elevated bilirubin due to Gilbert*s disease or a similar syndrome involving slow conjugation of bilirubin), ASAT and ALAT < 3 x ULN
• Renal function as defined by serum creatinine <= 1.5 x ULN or creatinine clearance >= 50 mL/min (by Cockcroft-Gault formula);
• Negative pregnancy test (urine/serum) for female patients with childbearing potential;
• Written informed consent

Exclusion criteria

• Any psychological condition potentially hampering compliance with the study

protocol
• Any treatment with investigational antitumor drugs within 28 days prior to receiving the first dose of investigational treatment; or within 21 days for standard chemotherapy; or within 14 days for weekly scheduled chemotherapeutic regimens or endocrine therapy
• Radiotherapy within the last four weeks prior to receiving the first dose of investigational treatment; except 1 or 2 x 8 Gy for pain palliation, then seven days interval after the last radiation should be maintained
• Known persistent (>4 weeks) >= Grade 2 toxicity from prior cancer therapy (except for alopecia grade 2)
• Symptomatic brain or leptomeningeal metastases. If adequately treated with resection and/or irradiation and patients are at least four weeks completely free of symptoms of these metastases without the use of corticosteroids, patients could be eligible
• Women who have a positive pregnancy test (urine/serum) and/or who are breastfeeding;
• Unreliable contraceptive methods. Women and men enrolled in this trial must agree to use a reliable contraceptive method throughout the study (adequate contraceptive methods are: intra-uterine devices or systems, condom or other barrier contraceptive measures, sterilization and true abstinence)
• Concomitant use with P-gp inhibitors or inducers or BCRP inhibitors
• Any known history of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML)
• Uncontrolled infectious disease (such as Human Immunodeficiency Virus HIV-1 or HIV-2 infection) or known active hepatitis B or C
• Recent myocardial infarction (< six months) or unstable angina

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-09-2019
Enrollment:	78

Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Talzene
Generic name:	Talazoparib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	17-07-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	16-09-2019
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-11-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-01-2024

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-08-2024
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

No registrations found.

In other registers

Register	ID
EU-CTR	CTIS2024-518036-36-01
EU-CTR	CTIS2024-518036-36-02
EudraCT	EUCTR2018-002914-10-NL
CCMO	NL66856.078.18