A feasibility study of niraparib for advanced, BRCA1-like, HER2-negative breast cancer patients: the ABC study

Published: 31-08-2016
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To establish whether niraparib single agent treatment in advanced BRCA1-like, HER2 negative breast cancer patients deserves to be further studied

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

Summary

ID

NL-OMON47829

Source
ToetsingOnline

Brief title
ABC study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, metastastic

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Tesaro

Intervention

Keyword: BRCA-1 like, breast cancer, metastatic

Outcome measures

Primary outcome

Progression-free survival rate at 4 months (PFSR-4m) as assessed according to

RECIST v1.1

Secondary outcome

* To determine objective response rate (according to RECIST v1.1)

* To determine duration of response

* To determine the clinical benefit rate (CR + PR + SD * 6 months)

* To determine median overall survival

* To determine safety and tolerability of niraparib single agent for

BRCA1-like, HER2-negative, advanced breast cancer patients

* Translational studies, e.g. putative resistance markers, like ex vivo RAD51

assay, 53BP1 protein expression, XIST gene expression, genetic reversal in the

case of a tumor BRCA1-mutation on tumor material obtained before start and

again after progression on niraparib, and discovery studies using whole genome

NGS, RNAseq etc.

Study description

Background summary

Evidence from preclinical and clinical studies has emerged that breast cancer cells deficient in homologous recombination to repair DNA double strand breaks (DSBs), as in BRCA1/2-mutated cells, offers a target for DNA DSB-inducing regimens, such as alkylating agents, platinum compounds or poly(ADP)ribose

polymerase (PARP) inhibitors. Recently, a putative companion diagnostic has been derived from the characteristic DNA copy number aberrations present in BRCA1-mutated breast cancers. This test has been coined the *BRCA1-like test*. BRCA1-like tumors comprise ±7.5% of all breast cancers5-7. BRCA1-like tumors can be divided into three groups: ± 25% have a BRCA1-mutation, ±35% have a BRCA1 promoter hypermethylation causing silencing of the BRCA1 gene, and for ± 40% the underlying molecular aberration is unknown. Circa 80-90% of BRCA1-like tumors are hormone receptor-negative, and HER2 negative (so-called *triple-negative*) breast cancers9. Within the triple-negative breast cancer subgroup, depending on the median age of the case mix, ± 50% of cases are BRCA1-like, which percentage is inversely correlated with median age.
The BRCA1-like test can be read out from both DNA (formalin-fixed, paraffin-embedded (FFPE) tumor material)10 or RNA (fresh frozen (FF) tumor material)11. The test is robust, reproducible and has shown clinical validity and utility as a companion diagnostic in selecting high-risk breast cancer patients for DNA DSB-inducing regimens, notably intensified alkylating chemotherapy (DNA-based test) and the combination of carboplatin/veliparib added to standard adjuvant chemotherapy (RNA- based test)12. Since the RNA-based BRCAness classifier has been shown to predict benefit from carboplatin/veliparib in the ISPy-2 study, we propose to use this classifier to select patients that are likely to benefit from niraparib.
Since no data exist on progression-free survival (PFS) of BRCA1-like metastatic breast cancer patients, we can only use the proxy of triple-negative breast cancers. Data from recently published studies suggests that the median PFS after first line treatment is ~ 6 months, and after second line treatment this is ~ 3 months. Recently, two studies reported on single agent olaparib activity in advanced BRCA-mutated and TNBC patients who had received a median of three prior chemotherapy regimens. Median PFS in the BRCA-mutated patients was 4-6 months17, and in the TNBC patients it was ± 2 months18. Unpublished preliminary data in PDX models suggest that besides BRCA-mutated breast cancers, also non-BRCA-mutated, BRCA1-like breast cancers may derive benefit from single agent PARP-inhibitors. In the currently proposed study we would like to investigate whether development of single agent PARP-inhibitors for incurable BRCA1-like breast cancer patients deserves to be further studied.
Treatment of patients with locally recurrent BRCA1-like, HER2-negative breast cancer that cannot be treated with curative intent by local treatment (surgery, radiotherapy +/- hyperthermia) or patients with metastatic BRCA1-like, HER2-negative breast cancer that have received a maximum of one prior line of treatment for incurable disease

Study objective

To establish whether niraparib single agent treatment in advanced BRCA1-like, HER2 negative breast cancer patients deserves to be further studied

Study design

Single arm, open-label, multicenter, phase II study with a Simon*s two-stage design

Study burden and risks

Burden and risks
1. Mandatory tumor biopsy before start of treatment.
2. Optional: 2 extra tumor samples (taken for the same location as mandatory tumor biopsy)
3. Additional blood samples
4. At start and every 2 cycles CT-chest/abdomen until progression
5. Extra hospital visits, specifically before start and during first treatment cycle.
6. Optional: tumor biopsy at Niraparib resistance
7. Optional: additional blood samples for ctDNA, NGS en research into immune modulation by PARP-inhibitors

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

* Histological proof of advanced, HER2 negative breast cancer;
* The tumor must be BRCA1-like, as identified by Agendia*s RNA-based BRCAness classifier;with a maximum of 25% of the study population in each stage.
* Only the following patients may be referred for BRCA1-like testing: all patients that had triple negative primary breast cancer; hormone-receptor positive, HER2-negative primary breast cancer patients with a histological grade III breast cancer; Breast cancer patients carrying a BRCA1 and/or BRCA2 germ line mutation.
* Pretreatment containing an anthracycline and/or taxane in the (neo-)adjuvant or metastatic setting received, or if not, then discussed with the patient whether it is justified to forego these treatments;
* Maximum of two prior lines of chemotherapy for advanced disease.
* Age * 18 years;
* Able and willing to give written informed consent;
* WHO performance status of 0, 1 or 2;
* Life expectancy * 3 months, allowing adequate follow up of toxicity evaluation and antitumor activity;
* Measurable or evaluable disease according to RECIST 1.1 criteria;
* Minimal acceptable safety laboratory values
-ANC of * 1.5 x 109 /L
-Platelet count of * 150 x 109 /L
-Hemoglobin * 10 g/dL (6.21mmol/L)
-Hepatic function as defined by serum bilirubin * 1.5 x ULN, ASAT and ALAT < 2.5 x ULN; Subjects who have obligatory liver toxic medication or liver steatosis should have values < 5 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.

Exclusion criteria

* Any systemic anticancer treatment within 14 days prior to receiving the first dose of investigational treatment; , except for endocrine therapy that may be continued up to 1 week before start niraparib
* Patienten met progressive op eerdere palliatieve behandeling met PARP1-remmers, platina bevattende behandeling of hoge dosis alkylerende middelen met stam cel transplanatatie.

Platinum-gevoelige of PARP1-remmer-gevoelige patienten die om andere reden dan progressive zijn gestopt zijn wel eligible;
* Patienten die hoge dosis alkylerende midelen met autologe stam cel transplantatie hebben gehad in (neo)adjuvante setting, tenzij deze behandleing meer dan 3 jaar geleden is gegeven;
*Voorbehandeling bevat geen anthracycline en/of taxane, in de (neo-) adjuvante of gemetastaseerde setting tenzij deze behandelingen gecontraindiceerd zijn;

Study design

Design

Study phase:	2
Study type:	Observational invasive
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-05-2018
Enrollment:	39
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Niraparib
Generic name:	Niraparib

Ethics review

Approved WMO

Date:	31-08-2016
Application type:	First submission

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-09-2017
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	12-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-04-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	15-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	21-08-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	02-09-2019
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	

Date:	18-02-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	19-02-2020
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

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	EUCTR2016-001852-23-NL
ClinicalTrials.gov	NCT02826512
CCMO	NL57676.031.16