# A phase III, randomized, open label, multicenter, controlled trial of niraparib versus physician*s choice in previously-treated, HER2 negative, germline BRCA mutation-positive breast cancer;patients

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Primary objective: To compare progression-free survival (PFS) as assessed by blinded, central review between patients randomized to niraparib versus physician*s choice. Key secondary objective: To compare overall survival between patients randomized...

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

## Summary

### ID

NL-OMON45039

**Source**
ToetsingOnline

**Brief title**
BRAVO

### Condition

- Breast neoplasms malignant and unspecified (incl nipple)

**Synonym**
breast cancer, lobular carcinoma

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** TESARO Inc.
**Source(s) of monetary or material Support:** farmaceutisch bedrijf/ sponsor

## Intervention

**Keyword:** BRCA-mutation positive, breastcancer, HER2-negative

## Outcome measures

### Primary outcome

The primary objective of this study is to determine the efficacy of niraparib compared to physician's choice amongst four single agent chemotherapy agents (eribulin, vinorelbine, gemcitabine or capecitabine) in treatment of patients with germline BRCA mutation with advanced/ metastatic HER2 negative breast cancer who have been treated with up to 2 prior lines of chemotherapy for advanced/ metastatic disease. This objective will be assessed by the primary endpoint of PFS as assessed by blinded, central review.

### Secondary outcome

Key secondary endpoint is evaluation of overall survival.

Safety and tolerability will be described using frequency of AEs and AEs of CTCAE grade *3. Safety analyses will include all patients who have received at least one dose of study drug and will be evaluated descriptively.

# Study description

### Background summary

Metastatic cancer is managed by various combinations of available treatments including surgery, radiation, chemotherapy, and targeted therapies. However, even with optimal treatment, 10-year survival rate is only about 10% (Ref. 2),

and therefore a significant unmet medical need exists for new therapies to treat patients with advanced/metastatic breast cancer.

## Study objective

Primary objective: To compare progression-free survival (PFS) as assessed by blinded, central review between patients randomized to niraparib versus physician*s choice.
Key secondary objective: To compare overall survival between patients randomized to niraparib versus physician*s choice.

## Study design

Phase III - superiority study. Randomization will be conducted with stratification for visceral disease (yes or no), histology (TNBC vs ER/PR positive) and number of lines of prior cytotoxic chemotherapy (not including hormonal therapy) for advanced/metastatic disease (0-1 or 2).
No crossover to niraparib is permitted following discontinuation from physician*s choice treatment.
Randomization will be 2:1 (treatment: control). At least 306 patients with germline BRCA mutations, as identified by the centralized test, will be randomized. The intent-to-treat population, defined as all randomized patients, is the primary analysis population for the efficacy analysis.

## Intervention

Group 1: niraparib 300 mg (3x100 mg niraparib capsules) will be administered orally QD continuously in an open- label fashion. Patients will be required to fast for at least 2 hours before each daily dose and for 2 hours after each daily dose.
Group 2: Physician's choice (amongst one of the following four single agents: eribulin, vinorelbine, gemcitabine or capecitabine) of chemotherapy will be administered in 3 week cycles. The physician*s choice chemotherapy must be designated prior to randomization of each patient.
Patients will continue on study medication until disease progression as long as in the investigator's opinion they are benefiting from treatment and do not meet any other treatment discontinuation criteria.

## Study burden and risks

The patient will be askes to come to the hospital regularly every 21 days for exams.
The patient will have (more) CT scans and MRI scans.
The patient will be asked to complete questionnaires.

# Contacts

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**Scientific**
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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. Histologically or cytologically confirmed HER2-negative metastatic or locally advanced breast cancer that is not amenable to resection or radiation with curative intent.;2. Female and male patients age at least 18 years.;3. Germline BRCA1 or BRCA2 mutation that is considered deleterious or suspected deleterious (include those mutations or translocations termed *deleterious* or *suspected deleterious* according to Myriad reporting) by analysis at a reference laboratory (Myriad Genetic Laboratories, Salt Lake City, UT, USA, or Myriad GmbH, Martinsried, Germany). ;4. Measurable disease by RECIST v1.1 or non- measurable disease that is clinically evaluable (except sclerotic-only bone disease; bone-only disease that has a lytic component is allowed).;5. Patients must not have symptomatic uncontrolled brain metastases To be considered controlled, central nervous system (CNS) disease must have undergone treatment (whole brain radiation, radiosurgery or equivalent) at least 1 month previously and the patient has no new or progressive signs or symptoms related to the CNS

disease, and are off steroid therapy two weeks. ;6. Up to 2 prior cytotoxic regimens for advanced or metastatic breast cancer (not including adjuvant or neo-adjuvant therapy); patients with no prior cytotoxic regimens for advanced or metastatic disease will only be allowed if they relapsed during or within 12 months of (neo-) adjuvant cytotoxic therapy.;7. Prior therapy should have included an anthracycline and a taxane (unless contraindication to those) in the neoadjuvant, adjuvant, or advanced/metastatic setting.;a. Hormone receptor positive patients must also have hormone resistant disease; either relapsed while on adjuvant endocrine treatment, or within one year of completing adjuvant endocrine treatment, or progression on at
least one line of endocrine treatment for advanced cancer.;8. Patients must not have received anticancer chemotherapy, radiotherapy, hormonal therapy, biological therapy, or any other investigational therapy within 3 weeks prior to the start of study treatment. Patients with persistent toxicity (except alopecia) > grade 1 from prior cancer therapy will also be excluded. Bisphosphonate and denosumab is allowed.;9. No prior treatment with a known or putative PARP inhibitor (except iniparib). No other anticancer agent (chemotherapy, hormonal therapy, or other agent) is to be permitted during the course of the study for any patient.;10. Patients who have previously received platinum chemotherapy in the metastatic setting are allowed to enroll in the study as long as they did not progress while on or within 8 weeks from the day of the last platinum administration. Patients who received platinum in the (neo-) adjuvant setting are eligible, as long as they relapsed 12 months or more after the last dose of platinum.;11. ECOG performance status 0-2 (Appendix G).;12. Adequate organ function (assessed within 72 hours prior to the first dose):;a. Absolute neutrophil count (ANC) * 1,500 cells/*L;b. Platelets * 100,000 cells/*L;c. Hemoglobin * 9 g/dL;d. Serum creatinine * 1.5 × upper limit of normal (ULN) or * 50 mL/min using Cockcroft-Gault equation;e. Total bilirubin * 1.5 × ULN OR direct bilirubin * ULN;f. Aspartate transaminase (AST) and alanine transaminase (ALT) * 2.5 × ULN or < 5 × ULN with liver metastases;13. Patients able to swallow and retain oral tablets;14. Female patients must not be pregnant or breast feeding;a. Female patient of childbearing potential must have a negative serum pregnancy test.;15. Patients of childbearing potential who are sexually active and their partners must agree to the use of a highly effective form of contraception throughout their participation during the study treatment and for 90 days after last dose of study treatment(s). ;16. No known hypersensitivity to the components of niraparib or any of its analogs.;17. No major surgery within 2 weeks prior to registration. Patients must have recovered from earlier major surgery before registration.;18. No prior diagnosis of Stage IV ovarian cancer ;-Patients with history of Stage III ovarian cancer must have a 5-year disease-free interval and a normal serum carcinoma antigen 125 (CA125);-Patients with Stage I or II ovarian cancer must have a disease-free interval of 2 years and a normal serum carcinoma antigen 125 (CA 125);19. No prior diagnosis, detection, or treatment of invasive cancer other than breast cancer within 2 years (except basal or squamous cell carcinoma of the skin that has been definitively treated);20. Patients must not be considered a poor medical risk due to a serious, uncontrolled medical disorder, non-malignant systemic disease, or active, uncontrolled infection. Examples include, but are not limited to uncontrolled ventricular arrhythmia, recent (within 3 months) myocardial infarction, uncontrolled major seizure disorder, unstable spinal cord compression, superior vena cava syndrome, or any psychiatric disorder that prohibits obtaining informed consent.;21. Absence of any psychological, familial, sociological or geographical condition potential hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient ;22. No

immunocompromised patients (e.g., patients who are known to be serologically positive for human immunodeficiency virus [HIV]). ;23. No patients with known active Hepatitis B or C. ;24. Patients should acknowledge that they are at an increased risk of infection with conventional chemotherapy drugs and since the effects with niraparib are unknown they must accept that live virus and bacterial vaccines should not be administered to them for the duration of the study and for 3 months after last dose of study medication. ;25. If patients are blood donors they should accept not to donate blood during the study and for 3 months after the last dose of study drug. ;26. Patients must have voluntarily agreed to participate by given informed consent. ;27. If all of the comparator treatments are contraindicated the patient will not be included in the trial. ;28. Patients must not have received a platelet transfusion within 4 weeks of the first dose of study treatment and must not have had any known, persistent (>4 weeks) * grade 3 hematological toxicity or fatigue from last cancer therapy. ;29. Patients must not have any known history of myelodysplastic syndrome (MDS). ;30. Patients must agree to peripheral blood samples during screening and at the end of treatment for mutational profile testing (for mutations of selected myeloid related genes) that will be performed only if the patient develops MDS or acute myeloid leukemia (AML) during the study or the post- treatment follow- up (a third sample will be collected in this case).

### Exclusion criteria

The selection criteria listed in the protocol summary and Section 3.2 of the protocol contain many exclusions; they are just stated as selection criteria.
The most important are:
- Patients must not have symptomatic uncontrolled brain metastases
- Patients must not have received anticancer chemotherapy, radiotherapy, hormonal therapy, biological therapy, or any other investigational therapy within 3 weeks prior to the start of study treatment. Patients with persistent toxicity (except alopecia) > grade 1 from prior cancer therapy will also be excluded. Bisphosphonate and denosumab is allowed.
- Patients must not be platinum resistant defined as: progression of cancer during or within 6 months of completion of prior platinum treatment.

## Study design

### Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

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| Control: | Active |
| Primary purpose: | Treatment |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 19-09-2014 |
| Enrollment: | 16 |
| Type: | Actual |

## Medical products/devices used

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|---|---|
| Product type: | Medicine |
| Brand name: | Capecitabine CF 150mg (Film-coated tablet) |
| Generic name: | Capecitabine |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | GEMCITABINE Sandoz 200mg (Powder for solution for infusion) |
| Generic name: | GEMCITABINE |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | PR1 |
| Generic name: | Niraparib |
| Product type: | Medicine |
| Brand name: | Vinorelbine Sandoz 10mg/ml (Concentrate for solution for infusion) / |
| Generic name: | Vinorelbine |
| Registration: | Yes - NL intended use |

# Ethics review

Approved WMO

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|---|---|
| Date: | 24-12-2013 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |

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|---|---|
| Approved WMO Date: | 20-02-2014 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 10-04-2014 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 24-04-2014 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 18-06-2014 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 20-06-2014 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 27-08-2014 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 24-07-2015 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 18-08-2015 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 06-11-2015 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO | |

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|---|---|
| Date: | 10-02-2016 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 25-02-2016 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 21-03-2016 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 16-08-2016 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 09-01-2017 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 22-03-2017 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 26-04-2017 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 08-05-2017 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 01-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO | |

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|---|---|
| Date: | 08-05-2018 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

# 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 | EUCTR2013-000684-85-NL |
| ClinicalTrials.gov | NCT01905592 |
| CCMO | NL47280.028.13 |