

# A phase I followed by a randomized phase II trial of two cycles carboplatin-olaparib followed by olaparib monotherapy versus capecitabine in BRCA-1 or -2 mutated Her2 negative advanced breast cancer as first line treatment (REVIVAL study)

Published: 15-10-2014

Last updated: 21-04-2024

Part 1: Determine the Recommended Phase II Dose

<b>Ethical review</b>	Approved WMO
<b>Status</b>	Recruitment stopped
<b>Health condition type</b>	Chromosomal abnormalities, gene alterations and gene variants
<b>Study type</b>	Interventional

## Summary

### ID

NL-OMON46924

### Source

ToetsingOnline

### Brief title

REVIVAL

### Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Breast neoplasms malignant and unspecified (incl nipple)

### Synonym

breast cancer, carcinoma of the breast

## Research involving

Human

## Sponsors and support

**Primary sponsor:** Antoni van Leeuwenhoek Ziekenhuis

**Source(s) of monetary or material Support:** Astra Zeneca, Farmaceutische Industrie

## Intervention

**Keyword:** BRCA1, BRCA2, carboplatin, olaparib

## Outcome measures

### Primary outcome

Part 1: Recommended Phase II dose.

### Secondary outcome

Part 1:

Pharmacokinetics of olaparib and carboplatin-olaparib

List of dose limiting toxicities

## Study description

### Background summary

Preclinical studies revealed that the combination of platinum compounds and olaparib is additive and possibly even synergistic in cell models with BRCA1 or -2 mutations. Early clinical trials suggested high benefit of olaparib with induction carboplatin in BRCA1 and -2 mutation carrier enriched populations. However, there is no evidence yet that carboplatin-olaparib has a superior benefit-risk compared to current standard therapy in advanced breast cancer in BRCA1 and -2 mutation carriers.

This study will consist of two parts. Part 1 is a dose escalation study of two cycles carboplatin and olaparib tablets. This is due to a formulation change of olaparib after the previous studies investigating this combination.

## **Study objective**

Part 1: Determine the Recommended Phase II Dose

## **Study design**

Part 1: Classical 3+3 dose escalation trial. The escalation schedule will start at carboplatin AUC3 and olaparib 25 mg bidaily. If this is found to be safe the dose will be escalated to carboplatin AUC4 and olaparib 25 mg bidaily, followed by increases in the olaparib dose to 50, 75 and 100 mg bidaily.

The schedule is 2 3-weekly cycles of carboplatin-olaparib combination therapy, according to the described escalation schedule, followed by olaparib monotherapy bidaily 300 mg until toxicity or disease progression. On day 0 and 1 patients will be hospitalized for pharmacokinetics blood sampling. Subsequently weekly check-ups will be done until stop of treatment. The last follow-up will occur 30 days after the end of treatment.

## **Intervention**

Part 1: carboplatin-olaparib followed by olaparib monotherapy (300 mg bidaily)

On day 0 and 1 blood sampling for pharmacokinetics will take place.

Day 0 : predose, 0.5, 1,2,4,6,8,10,12

Day 1 : predose, 0.5, 1,2,2.25,2.5, 3,4,6,8, 10,12,

Day 2 : 24 hours after predose day 1

Day 3 : 48 hours after predose day 1

Day 8: 1 sample PD

On day 0 and 1 patients will take one dose of olaparib, followed by bidaily olaparib doses for the rest of treatment.

On day 1 of cycle 1 and 2 carboplatin will be administered intravenously.

Check-ups are weekly in cycle 1 to 4. From cycle 5 onwards check-ups will take place 3-weekly.

## **Study burden and risks**

Possible risks with venapunctures is the development of a hematoma at the place of venapuncture. Possible risks of tumor biopsies are mild pain during anesthesia and the place where the biopsy is taken can become sensitive and mildly painful during a few days. With biopsies from pulmonary tissue, there is a slight risk of a pneumothorax.

Olaparib is not registered. Main toxicities are grade 1/2 haematological toxicities, nausea and vomiting, diarrhoea, dyspepsia, fatigue, dizziness. In

particular a combination with another bone marrow suppressing drug such as carboplatin it is expected that the overlapping toxicity will result in more pronounced haematological toxicity.

Carboplatin is not registered for treatment of advanced breast cancer, but is a well-known drug in treatment of, for example ovarian cancer. The dose limiting toxicity of carboplatin is myelosuppression (leukocytopenia, thrombocytopenia and anaemia), which in general is reversible and not cumulative in the case of monotherapy at recommended frequency of administration. Other common side effects include nausea and vomiting and asthenia. Subclinical liver and renal function impairment and electrolyte abnormalities frequently occur.

Dose limiting toxicities of capecitabine are gastrointestinal toxicities (diarrhoea, abdominal pain, nausea, stomatitis) and hand-foot syndrome.

The burden associated with the study is more than standard in part 1. In particular, patients are hospitalized for a small amount of pharmacokinetic blood sampling. Safety follow-up is more frequent than standard, occurring every week instead of every three weeks.

## Contacts

### **Public**

Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121  
Amsterdam 1066 CX  
NL

### **Scientific**

Antoni van Leeuwenhoek Ziekenhuis

Plesmanlaan 121  
Amsterdam 1066 CX  
NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

### Age

Adults (18-64 years)

Elderly (65 years and older)

### Inclusion criteria

1. Histological or cytological proof of advanced cancer pre-treated with maximally one line of systemic chemotherapy in the advanced setting and any line of hormonal therapy for advanced disease, and potentially benefitting from olaparib-carboplatin combination therapy; (prior (neo-) adjuvant chemotherapy is accepted and does not count as one line, since administered in early stage disease);
2. Age  $> \leq 18$  years;
3. Able and willing to give written informed consent;
4. WHO performance status of 0, 1 or 2;
5. Able and willing to undergo blood sampling for PK and PD analysis;
6. Life expectancy  $> 3$  months, allowing adequate follow up of toxicity evaluation and antitumor activity;
7. Evaluable disease according to RECIST 1.1 criteria;
8. Minimal acceptable safety laboratory values
  - a. ANC of  $> 1.5 \times 10^9 /L$
  - b. Hemoglobin of at least 6.2 mM and no transfusion within 28 days
  - c. Platelet count of  $> 100 \times 10^9 /L$
  - d. Hepatic function as defined by serum bilirubin  $< 1.5 \times ULN$  (or  $< 3 \times ULN$  in case of known Gilbert syndrome) , ASAT and ALAT  $< 2.5 \times ULN$  (or  $< 5 \times ULN$  in case of liver metastasis)
  - e. Renal function as defined by serum creatinine  $< 1.5 \times ULN$  or creatinine clearance  $> 50$  mL/min (by Cockcroft-Gault formula);
9. Negative pregnancy test (urine/serum) for female patients with childbearing

### Exclusion criteria

1. Any treatment with investigational drugs within 28 days prior to receiving the first dose of investigational treatment; or 21 days for standard (neo-)adjuvant chemotherapy, hormonal and immunotherapy;
2. Patients who have received high dose alkylating agents or a PARP1 inhibitor or carboplatin pretreatment; unless no progression on carboplatin had been observed during earlier treatment and the last carboplatin administration had been longer than 6 months ago.
3. Any current treatment with drugs that induce or inhibit the CYP3A4 system : <http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionlabeling/ucm093664.htm#inVivo> or APPENDIX IX
4. Women who have a positive pregnancy test (urine/serum) and/or who are breast feeding;
5. 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: oral, injected or implanted hormonal methods, intra-uterine devices or systems, condom or other barrier contraceptive measures, sterilization and true abstinence)

6. Radiotherapy within the last four weeks prior to receiving the first dose of investigational treatment; except 1x8 Gy for pain palliation then a seven days interval should be maintained;

7. Uncontrolled infectious disease or known Human Immunodeficiency Virus HIV-1 or HIV-2 type patients;

8. Patients with known active hepatitis B or C;

9. Recent myocardial infarction (< six months) or unstable angina;

10. Symptomatic brain metastases. If adequately treated with resection and/or irradiation and patients are at least four weeks completely free of symptoms of these metastases and without medication related to these metastases patients could be eligible if all other in- and exclusion criteria are obeyed.

11. Known leptomeningeal metastases.

12. Patients with myelodysplastic syndrome or acute myeloid leukemia

13. Any medical condition not yet specified above that is considered to possibly, probably or definitely interfere with study procedures, including adequate follow-up and compliance and/or would jeopardize safe treatment.

## Study design

### Design

**Study type:** Interventional

Masking: Open (masking not used)

Control: Uncontrolled

Primary purpose: Treatment

### Recruitment

NL

Recruitment status: Recruitment stopped

Start date (anticipated): 07-05-2015

Enrollment: 20

Type: Actual

### Medical products/devices used

Product type: Medicine

Brand name: nvt

Generic name:	carboplatin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	nvt
Generic name:	olaparib

## Ethics review

Approved WMO	
Date:	15-10-2014
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	10-02-2015
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	15-10-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	13-11-2015
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	27-06-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	29-06-2018
Application type:	Amendment

Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	30-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	31-08-2018
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO	
Date:	28-03-2019
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	EUCTR2013-005590-41-NL
CCMO	NL50610.031.14



## Study results

Results posted: 28-05-2021

**First publication**  
21-12-2020