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

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	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 venapunctions is the development of a heamatoma at the place of venapunction. Possible risks of tumor biopsies are mild pain during anasthesia and the place where the biopsy is taken can become sensitive an 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

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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. 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 ><= 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 x 10^9 /L
b. Hemoglobin of at least 6.2 mM and no transfusion within 28 days
c. Platelet count of > 100 x 10^9 /L
d. Hepatic function as defined by serum bilirubin < 1.5 x ULN (or <3 xULN in case of known Gilbert syndrome) , ASAT and ALAT < 2.5 x ULN (or <5 xULN in case of liver metastasis)
e. Renal function as defined by serum creatinine < 1.5 x 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/druginteractionslabeling/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 myelodysplatic 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