Olaparib dose escalation in combination with high dose radiotherapy to the breast and regional lymph nodes in patients with breast cancer

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To define the maximal tolerated dose (MTD) of olaparib in combination with radiotherapy of the breast and regional lymph nodes in patients with breast cancer without the use of skin bolus (arm A) or with the use of skin bolus (arm B).

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

Summary

ID

NL-OMON44691

Source
ToetsingOnline

Brief title
Olaparib combined with radiotherapy in breastcancer patients

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, metastatic breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut

Source(s) of monetary or material Support: Astra Zeneca,subsidie van AstraZeneca

Intervention

Keyword: breastcancer, olaparib, radiotherapy

Outcome measures

Primary outcome

The incidence of dose limiting toxicities.

Secondary outcome

* Acute toxicity: severity, duration and relation with treatment of all adverse events according to CTCAE version 4.03 occurring from start of treatment until 3 months after end of treatment

* Late toxicity: severity, duration and relation with treatment of all adverse events that are possibly, probably or definitely related to the combination treatment according to CTCAE version 4.03 occurring from 3 months until 2 years after end of treatment

* PK variables: steady state AUC, steady state C-max, steady state C-min

* Pd variables: PARP inhibition in PBMCs and tumor biopsies; *H2AX foci formation upon ex vivo irradiation in PBMCs & circulating tumor cells

* Objective response rate at 3 months after end of treatment assessed by RECIST version 1.1 using MRI-mamma ((only in patients with the tumor present in the breast)

* Locoregional control in patients with the tumor present in the breast as assessed by physical examination and if clinically indicated supported by radiological and/or pathological investigations in postoperative patients as assessed by routine follow-up investigations (i.e. physical examination and

radiological investigations), confirmed by pathology report(s)

* Localisation of recurrences in relation to the planned radiotherapy fields:

PTV & boost PTV

Study description

Background summary

Breast cancer is the most frequent occurring malignancy in Dutch women with over 13,000 new diagnoses per year. The majority of breast cancer patients receive radiotherapy as part of their treatment. Radiotherapy improves both locoregional control and overall survival.

Radiotherapy kills tumor cells by inducing DNA damage. The effect of radiotherapy is limited by the ability of tumor cells to repair this DNA damage. In base excision repair and single strand break DNA repair, poly(ADP-ribose)polymerase (PARP) is an important enzyme initiating DNA repair. In preclinical in vitro and in vivo studies, PARP inhibition and consequently inhibition of PARP-facilitated DNA repair enhances the anti-tumor activity of radiotherapy.
Olaparib is a potent PARP inhibitor developed as an anti-cancer drug for HR defected tumors and as a dose intensifier for chemo- and radiotherapy. The combination of olaparib and radiotherapy is expected to improve locoregional control and thereby overall survival.

However, this combination treatment has never been tested in humans before. The purpose of this study is to determine the safety and tolerability of radiotherapy to the breast and regional lymph nodes with concurrent olaparib.

Study objective

To define the maximal tolerated dose (MTD) of olaparib in combination with radiotherapy of the breast and regional lymph nodes in patients with breast cancer without the use of skin bolus (arm A) or with the use of skin bolus (arm B).

Study design

This is an open-label, dose-escalating, non-randomized, single-centre phase I study of olaparib combined with radiotherapy to the breast and regional lymph nodes in patients with inoperable, metastatic and/or inflammatory breast cancer with an indication for breast irradiation. Dose escalation of olaparib will be

done separately in two different patients groups due to expected differences in toxicity.

Dose escalation is performed using a time-to-event continuous-reassessment-model (TITE-CRM) design.
Dose escalation will be done in arm A and arm B separately using a separate dose level * DLT model to determine the MTD for each arm.

In each arm the first three patients will be treated at the starting dose level (in arm A 50mg BID, in arm B 25mg BID). Thereafter, patients will be assigned to a dose level using the TITE-CRM method in each arm separately and allowing for the following dose escalation restrictions:
1. A patient may not be assigned to a dose level unless at least three patients have completed the minimal follow-up time of 3 months after end of treatment at the dose level below.
2. The assigned dose level may not increase more than 1 level between consecutive patients. There is no restriction on the decrease in the number of levels between patients.

The total DLT evaluation period for each patient is from start of treatment until end of 1 year after end of treatment. See paragraph 4.3 for more details on TITE-CRM.

Intervention

1)
Radiotherapy to the whole breast and regionale lymph nodes: 46.69 Gy in 23 fractions.
In the post-operatieve setting the dose is 42.56 Gy (noindication for boost) and 46.20Gy (with the indication for an additional boost)
A SIB of 14.49 Gy as a boost. to the macroscopic tumor. Total dose: 61.18 Gy in 23 fractions.
Both indications to be completed with an additional radiation of the lymph nodes (if indicated)

2)
Olaparib: starting dose level: arm A: 50 mg BID; arm B: 25 mg BID

Study burden and risks

Patients will suffer side effects from the standard radiation treatment and on top of that the potential side effects caused by adding Olaparib . These side effects are not yet known. Participation in this study will not increase the number of follow-up visits and physical examinations, but during the regular blood tests additional blood sample will be taken for research purposes for which an additional informed consent is required.

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

For group A and B
1. *18 years of age
2. Patients should fulfill all inclusion criteria for patients with the tumor present in the breast (listed under point 3) OR all inclusion criteria for postoperative patients (listed under point 4)
3. For patients with the tumor present in the breast:
a. Histological proven breast cancer or local recurrence of breast cancer which is inoperable or/and metastatic, including inflammatory breast cancer
b. Tumor in breast accessible for biopsy
4. For postoperative patients:
a. Histological proven BC
b. Mastectomy or lumpectomy that is radical or focal irradical after (re-) excision
c. High risk of locoregional recurrence defined as:

- cN2-3 & (y)pN1-3 & non-operated pre-chemo, or pre-operative in case no neoadjuvant chemotherapy is given, PET-positive or PA-proven lymph nodes;
- or as judged by both the principle investigator and the treating physician
5. WHO performance 0-2
6. Life expectancy of at least 6 months
7. Adequate hematological, renal and hepatic functions
a. Hemoglobin * 6.2 mmol/l
b. Leucocytes * 3.0 x 10E9/l
c. Absolute neutrophil count * 1.5x10E9/l
d. Platelet count * 100 x 10E9/l
e. Total bilirubin * 1.5 x ULN
f. ASAT/ALAT * 2.5 x ULN ; or in the presence of liver metastases * 5 x ULN
g. Creatinine clearance * 50 ml/min; measured or calculated
8. Evidence of non-childbearing status for women of childbearing potential: negative urine or serum pregnancy test within 21 days of study treatment. Non-childbearing potential or postmenopausal is defined as:
* Amenorrheic for 1 year or more following cessation of exogenous hormonal treatments
* LH and FSH levels in post menopausal range for women under 50 years of age
* Radiation-induced oophorectomy with last menses > 1 year ago
* Chemotherapy-induced menopause with > 1 year interval since last menses
* Surgical sterilisation (bilateral oophorectomy or hysterectomy)
9 Patients of reproductive potential must agree to practice two effective medically approved contraceptive method during the trial and 3 months afterwards
10. Signed written informed consent
For arm A only:
11a Indication for breast irradiation without the use of skin bolus
For arm B only:
11b Indication for breast irradiation with the use of skin bolus

Exclusion criteria

1. Anti-cancer therapy including chemotherapy, radiotherapy, immunotherapy or use of other investigational agents within 3 weeks prior to start of therapy (or a longer period depending on the defined characteristics of the agents used e.g. 6 weeks for mitomycin ornitrosourea). Patient may continue the use of tamoxifen, aromatase inhibitor and LHRH agonists for cancer; bisphosphonates for bone disease and corticosteroids. The use of denosumab for bone disease is not allowed.
2. Major surgery within two weeks of starting study treatment.
3. Participation in other trial with investigational drug or treatment modality
4. Patients with symptomatic uncontrolled brain metastases. A scan to confirm the absence of brain metastases is not required.
5. Prior ipsilateral radiotherapy to the chest or breast.
6. Blood transfusion in the four weeks prior to study entry
7. Persistent toxicities (CTC * grade 2) with the exception of alopecia, caused by previous cancer therapy

8. QT-interval >470 msec
9. Significant cardiovascular disease as defined by
a. History of congestive heart failure defined as NYHA class III
b. History of unstable angina pectoris or myocardial infarction up to 3 months prior to trial entry;
c. Presence of severe valvular heart disease
d. Presence of a ventricular arrhythmia requiring treatment;
e. Uncontrolled hypertension
10. Patients considered a poor medical risk due to:
a. non-malignant systemic disease
b. active, uncontrolled infection requiring parenteral antibiotics
c. a serious, uncontrolled medical disorder; examples include, but are not limited to:
i. uncontrolled major seizure disorder
ii. unstable spinal cord compression
iii. superior vena cava syndrome
iv. extensive bilateral lung disease on HRCT scan
v. any psychiatric disorder that prohibits obtaining informed consent.
11. Any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule.
12. Patients who are known to be serologically positive for human immunodeficiency virus (HIV) and are receiving antiviral therapy.
13. Patients with known active hepatic disease (i.e. Hepatitis B or C)
14. Patients with myelodysplastic syndrome/acute myeloid leukaemia or features suggestive of MDS/AML on peripheral blood smear.
15. Gastrointestinal disorders that may interfere with absorption of the study drug or patients who are not able to take oral medication
16. Concomitant medications:
a. Any previous treatment with a PARP inhibitor, including Olaparib
b. Patients receiving the following classes of inhibitors of CYP3A4 (see Section 7.4 for guidelines and wash out periods)
i. Azole antifungals
ii. Macrolide antibiotics
iii. Protease inhibitors
17. Pregnant or breast-feeding women
18. Breast feeding women

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):	21-10-2013
Enrollment:	72
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Olaparib
Generic name:	Olaparib

Ethics review

Approved WMO Date:	19-06-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	05-08-2013
Application type:	First submission
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	29-04-2014
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	06-07-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)

Approved WMO Date:	25-08-2016
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	30-06-2017
Application type:	Amendment
Review commission:	PTC Stichting het Nederlands Kanker Instituut - Antoni van Leeuwenhoekziekenhuis (Amsterdam)
Approved WMO Date:	03-07-2017
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	EUCTR2011-001586-40-NL
ClinicalTrials.gov	NCT02227082
CCMO	NL36278.031.13