Substantially improving the cure rate of high-risk BRCA1-like breast cancer patients with personalized therapy (SUBITO) an international randomized phase III trial

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This study has been transitioned to CTIS with ID 2024-516196-32-00 check the CTIS register for the current data. To investigate whether (neo)adjuvant systemic treatment of intensified alkylating chemotherapy with peripheral stem cell rescue (mini-...

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

Summary

ID

NL-OMON56057

Source
ToetsingOnline

Brief title
SUBITO

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Nederlands Kanker Instituut
Source(s) of monetary or material Support: Astra Zeneca,KWF;ZonMw

Intervention

Keyword: BRCA-1 like, breast cancer, neo-adjuvant

Outcome measures

Primary outcome

Primary endpoint is overall survival defined as the time from randomization to death from any cause.in all patients

Secondary outcome

Key secondary endpoint:

Overall survival, defined as the time from randomization to death from any cause in patients without a germline BRCA1/2 mutation.

Other Secondary endpoints:

A - recurrence-free interval defined as time from randomization to invasive ipsilateral breast tumor recurrence, locoregional- or distant recurrence, or death from breast cancer, whichever comes first in all patients, regardless of germline BRCA1/2 status

B - recurrence-free interval defined as time from randomization to invasive ipsilateral breast tumor recurrence, locoregional- or distant recurrence, or death from breast cancer[27], whichever comes first, in patients with an HR impaired tumor (i.e. harboring a BRCA1-like copy number profile or BRCA1 promotor hypermethylation, in the absence of a known germline BRCA1/2

mutation).

C - (non-)hematological toxicity determined according to CTCAE v4.03

D - cost-effectiveness measured by costs per quality-adjusted life years

(QALYs) and incremental cost-effectiveness ratio (ICER).

E - Patient reported outcomes; including quality of life (QoL) determined by a

comprehensive panel of QoL questionnaires

F - several potential biomarkers, e.g.:

cell-free circulating tumor DNA

tumor educated platelets RNA

cancer immune interaction and reconstitution

XIST expression by primary tumor

53BP1 tumor expression of primary tumor

Functional ex-vivo RAD51 assay

Circulating tumor cells in peripheral blood stem cell (PBSC) harvest

G - The difference in overall survival between patients treated in the SUBITO

trial and patients with the same characteristics treated outside of the trial

in the Netherlands (using data from the Netherlands Cancer Registry (NCR)).

Study description

Background summary

The prognosis of women with high-risk breast cancer is still poor (stage III: 10-year survival of 30-40%). Current guidelines for adjuvant systemic treatment make no distinction between stage II or stage III breast cancer, due to a lack of personalized treatments and companion diagnostics.

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 cancers. In a retrospective analysis the BRCA1-like test appeared a promising companion diagnostic for adjuvant intensified alkylating (IA) chemotherapy (CT) in stage III breast cancer patients. In BRCA1-like patients the 7-year recurrence-free survival improved from 30% with standard CT to 78% with IA CT (adjusted hazard rate (HR) 0.12; p=0.001), while no benefit was observed in non-BRCA1-like patients6. These striking data asked for further exploration, and were confirmed by two other retrospective studies (adjusted HR 0.15; p=0.03 and adjusted HR 0.18; p=0.003).

In addition, there are strong indications that a PARP inhibitor is active in BRCA1-like breast cancers. Currently, olaparib is being investigated in the adjuvant setting in BRCA-mutated, triple negative breast cancer patients. Patients who have completed standard adjuvant chemotherapy are randomized between 1-year olaparib monotherapy and 1-year placebo (OlympiA trial: NCT02032823). To avoid generating results that will be outdated in 5-years* time, 1-year olaparib monotherapy will be added to the optimal standard-dosed treatment arm in the SUBITO trial.

Study objective

This study has been transitioned to CTIS with ID 2024-516196-32-00 check the CTIS register for the current data.

To investigate whether (neo)adjuvant systemic treatment of intensified alkylating chemotherapy with peripheral stem cell rescue (mini-CTC) compared to AC-CP chemotherapy followed by 1-year olaparib monotherapy substantially improves overall survival (OS) in stage III BRCA1-like breast cancer patients.

Study design

Investigator-initiated, international, multicentre, randomized, open-label, (neo)adjuvant phase III study in target population (stage III, HER2-negative, BRCA1-like breast cancer patients) comparing optimized standard-dose chemotherapy with intensified, alkylating chemotherapy with stem cell rescue.

Intervention

Both study arms:

3 x ddAC q 2 weeks
doxorubicin 60 mg/m² as an i.v. bolus and cyclophosphamide 600 mg/m² as an i.v. bolus on day 1 every 2 weeks
ddAC must be supported with prophylactic pegfilgrastim 6 mg s.c. given 24-48 hours after completion of administration of EVERY chemotherapy cycle

Experimental arm: 2 x IA CT q 3-4 weeks:
Stem cell mobilization
4th ddAC cycle with G-CSF *300 ug sc for 8-10 days according to local protocols
leukapheresis days 10-14 according to local protocols

intensified alkylating *mini* CTC (2x)
cyclophosphamide 3000 mg/m2 day 1
mesna 500 mg (push) + 2000 mg in 24 hours day 1
carboplatin (400 mg/m2; (or AUC=5 in patients with a calculated creatinine-clearance of <100 ml/min)) days 1,2
thiotepa 250 mg/m2 day 2

AC-CP-olaparib:
Patients will receive a 4th cycle of ddAC, followed by carboplatin/paclitaxel (CP) consisting of carboplatin (AUC 6) on day 1 and paclitaxel (80 mg/m2) on day 1,8 and 15 of a 21 days cycle. In total 4 courses of CP will be administered. Olaparib will be administered as monotherapy for one year at a dose of 300 mg BID, starting 3 weeks after adjuvant radiotherapy, or, if radiotherapy is not indicated, 3-5 weeks after the last CP cycle.

Capecitabin:
Patients in both arms that do not achieve a (near) complete pathologic response (pCR) in neoadjuvant setting will receive adjuvant capetcitabine in addition to their allocated study treatment.
Adjuvant capecitabine at a starting dose of 1000-1250 mg/m2, twice a day, on days 1-14 every 3 weeks for eight cycles. In case of DPYD-deficiency a dose reduction is recommended depending on the DPYD variant.

After IA CT or AC-CP:
Patients will undergo radiotherapy, if indicated.
Endocrine treatment for at least 5 years (according to the most recent Dutch national guidelines), starting 1 to 6 weeks after radiotherapy for patients with positive estrogen and/or progesterone receptors.

Study burden and risks

Blood will be drawn for biomarker research, hematology, and serum chemistry. Patients are at risk for development of doxorubicin-, cyclophosphamide-, carboplatin-, paclitaxel-, thiotepa-, and olaparib or capecitabin-related side effects (depending on the actual treatment administered). Patients in the treatment arm with leukapheresis and stem cell rescue are at risk for venous

catheter-related complications, and intensified alkylating chemotherapy with autologous stem cell rescue-related complications.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Women and men with stage III adenocarcinoma of the breast harboring signs of a breast cancer with features of homologous recombination deficiency (HRD)
- Age of 18-65 years
- The tumor must be HER2-negative
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1

Exclusion criteria

- Distant metastases
- Previous radiation therapy
- Previous chemotherapy
- Any previous treatment with a PARP-inhibitor, including olaparib
- Pre-existing neuropathy from any cause in excess of Grade 1
- Chronic concomitant use of known strong or moderate CYP3A inducers

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-01-2017
Enrollment:	94
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin Hospira
Generic name:	Carboplatin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Doxorubicin

Generic name:	Doxorubicin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Endoxan
Generic name:	Cyclophosphamide
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Lederthepa
Generic name:	Thiotepa
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Paclitaxel Hospira
Generic name:	Paclitaxel
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	15-09-2016
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-10-2016
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-07-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2017
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2018

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-10-2018
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	16-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	29-10-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-11-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-05-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-02-2022

Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-02-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	31-03-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-04-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	03-05-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-10-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	30-11-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	06-06-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	04-07-2024

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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
EU-CTR	CTIS2024-516196-32-00
EudraCT	EUCTR2016-002493-13-NL
ClinicalTrials.gov	NCTnummervolgt
CCMO	NL58091.031.16