Image-guided de-escalation of neoadjuvant chemotherapy in HER2-positive breast cancer: the TRAIN-3 study.

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This study has been transitioned to CTIS with ID 2024-516205-23-00 check the CTIS register for the current data. To evaluate efficacy of image-guided de-escalating chemotherapy in the presence of dual HER2-blockade with Herceptin® and pertuzumab in...

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

Summary

ID

NL-OMON54506

Source
ToetsingOnline

Brief title
TRAIN-3

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer; HER2 positive breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: BOOG Study Center

Source(s) of monetary or material Support: door BOOG ,Roche

Intervention

Keyword: breast cancer, de-escalation, HER2 positive, neoadjuvant

Outcome measures

Primary outcome

• Event-free survival (EFS)

Secondary outcome

• Overall survival

• Pathologic complete response in breast and axilla

• Radiologic complete response

• Number over neoadjuvant chemotherapy cycles administered

• Safety and exploratory translational outcomes

Study description

Background summary

High pathological complete response (pCR)-rates are seen using different neoadjuvant chemotherapy schedules with trastuzumab and pertuzumab in HER2-positive stage II-III breast cancer patients. Total pCR rates in breast and axilla have been described as high as 64%, and with an even higher rate of >80% in patients with HER2-positive and hormone receptor (HR) negative tumors. PCR is associated with better long-term outcomes in patients with HER2-positive breast cancer. Three year progression-free survival ranges between 85-90%. Neoadjuvant treatment of HER2-positive breast cancer typically consists of six to nine cycles of treatment. Longer duration of treatment is associated with higher pCR-rates but gives more toxicity. Pathological complete responses are sometimes seen after only 10-12 days of neoadjuvant treatment. It is therefore important to investigate which patients can safely be treated with less than six cycles of chemotherapy and who requires more than six cycles for maximum activity.
The radiologic response of a breast tumor after neoadjuvant therapy is predictive of the pathologic response, although the accuracy differs between

breast cancer subtypes. It is hypothesized that patients with an early complete radiologic response may not benefit from additional chemotherapy and can be referred for early surgery. Patients who have not achieved pCR after early surgery despite radiologic complete response (rCR) are candidates for further adjuvant chemotherapy to complete the initially planned number of treatment cycles and maintain maximum treatment activity. Imaged guided de-escalation in which the number of treatment cycles is determined by the radiologic response could thus reduce toxicity in neoadjuvant treatment while maintaining activity. Patients who do not have a pathologically complete response after neoadjuvant treatment are candidates for treatment with T-DM1. This gives a predicted invasive disease-free survival of 11%.
This study will evaluate the efficacy of image-guided de-escalation of neoadjuvant chemotherapy in patients with HER2-positive breast cancer.

Study objective

This study has been transitioned to CTIS with ID 2024-516205-23-00 check the CTIS register for the current data.

To evaluate efficacy of image-guided de-escalating chemotherapy in the presence of dual HER2-blockade with Herceptin® and pertuzumab in HER2-positive breast cancer, as measured by three-year event-free survival.
Secondary objectives
• To evaluate 3-year overall survival
• To evaluate pCR rate in breast and axilla
• To evaluate 5-year, and 10-year overall and event-free survival rate
• To evaluate the association between pCR and long-term outcome
• To evaluate the association between radiologic complete response (rCR) and pCR
• To compare short-term and long-term efficacy by number of chemotherapy cycles received
• To compare non-radical resection percentages between rCR and no rCR•
• To evaluate the association between VACBs and pCR
• To evaluate QoL after 3, 6 or 9 courses of chemotherapy

Study design

This is a multicenter, single arm, phase II study evaluating the efficacy of image-guided de-escalating neoadjuvant treatment with paclitaxel, Herceptin® (trastuzumab), carboplatin, and pertuzumab (PTC-Ptz) in stage II-III HER2-positive breast cancer.
The primary endpoint of the study is the 3-year event-free survival rate. Event-free survival will be calculated from time of registration to time of first event. An event is defined as the earliest occurrence of disease progression resulting in inoperability, invasive locoregional recurrence, distant metastases, or death from any cause. Patients alive without an event as of the analysis cutoff date will be censored at last study follow-up date.

Treatment regimen
The PTC-Ptz regimen consists of a maximum of nine cycles consisting of:
• Paclitaxel 80mg/m2 administered intravenously on day 1 and day 8
• Herceptin® 6mg/kg administered intravenously on day 1 (loading dose 8mg/kg) or Herceptin® administered subcutaneously 600mg on day 1
• Carboplatin AUC 6mg•ml/min administered intravenously on day 1
• Pertuzumab 420mg administered intravenously on day 1 (loading dose 840mg)
• Treatment cycles are repeated on day 22

Intervention

Number of neoadjuvant courses PTC-Ptz depends on the radiological response during the tumor evaluation every 3 courses. The total number of chemotherapy treatments depends on the eventual pathological complete response.

In addition to trastuzumab in the adjuvant setting pertuzumab is also given a total of one year.

All patients with pCR continue with Herceptin® (trastuzumab) and pertuzumab after surgery for a total of 12 months.
Patients who do not have pCR receive 14 cycles of adjuvant TDM1

Study burden and risks

All investigational products are registered for the neoadjuvant treatment of HER2-postive breast cancer and considered regular care. Adjuvant pertuzumab and TDM1 are not standard of care and will be provided until reimbursement.
Patients are at risk of developing treatment related toxicity. SAEs will be monitored. Blood will be drawn for translational research, hematology and chemistry.
Burden:
• Up to one or two times more often an MRI-scan of the breast and possibly an ultrasound scan of the axilla.
• Take a biopsy of a lymph node of the axilla max. one or two times more often than usual (this applies only to patients with proven lymph node metastasis at diagnosis or in case of doubt to newly developed suspected lymph nodes)
• Treatment with pertuzumab up to one year after the start of treatment.
• When participating in biomarker research: three additional tumor biopsies after three courses of therapy. *
• When participating in biomarker research: extra tubes of blood are drawn at four timepoint simultaneously with the regular blood collection (before the treatment, after one treatment, after three courses and before the operation) *
• VACBs will be taken in HR-positive patients with an early rCR to improve the NPV of imaging alone to predict pCR. VACBs gives a small risk of hematoma, bleeding or bruising.
• patients will be asked to fill in quality of life questionnaires four times

in total *

* If permission has been given separately

Contacts

Public
BOOG Study Center

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Scientific
BOOG Study Center

Moreelsepark 1
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NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histologically confirmed primary infiltrating breast cancer.
2. Stage II or III disease.
3. Overexpression and/or amplification of HER2 in an invasive component of the core biopsy.
4. Age <:18
5. ECOG Group performance status
6. LVEF >50% measured by echocardiography, MRI or MUGA

7. Known HR-status (in percentages)

Exclusion criteria

1. Previous chemotherapy
2. Pregnancy or breastfeeding
3. Evidence of distant metastases
4. Evidence of bilateraal infiltrating breast cancer
5. Concurrent anti-cancer treatment or another investigational drug

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	09-04-2019
Enrollment:	462
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Carboplatin
Generic name:	carboplatine
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Herceptin
Generic name:	trastuzumab

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kadcyla
Generic name:	Trastuzumab-emtansine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Perjeta
Generic name:	pertuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Taxol
Generic name:	paclitaxel
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	08-01-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	07-02-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	23-05-2019
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	05-06-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-08-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-02-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-03-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-05-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-01-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	04-01-2024
Application type:	Amendment

Review commission:	METC NedMec
Approved WMO Date:	09-01-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-04-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	09-08-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	24-09-2024
Application type:	Amendment
Review commission:	METC NedMec

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	CTIS2024-516205-23-00
EudraCT	EUCTR2018-003275-35-NL
ClinicalTrials.gov	NCT03820063
CCMO	NL66887.031.18