Neoadjuvant trastuzumab, pertuzumab and tucatinib without chemotherapy in HER2-positive breast cancer: the TRAIN-4 study

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This study has been transitioned to CTIS with ID 2024-518192-61-00 check the CTIS register for the current data. To evaluate safety and feasibility of neoadjuvant chemotherapy-free regimen with trastuzumab, pertuzumab and tucatinib in stage II-III…

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

Summary

ID

NL-OMON53609

Source
ToetsingOnline

Brief title
TRAIN-4

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer, HER2-positive breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: Seagen Inc. (volledige dochteronderneming van Pfizer Inc.)

Intervention

Keyword: Breastcancer, De-escalation, HER2-positive, Neoadjuvant

Outcome measures

Primary outcome

Incidence and severity of adverse events (all grades) until 30 days after last study treatment administration.

Secondary outcome

- Incidence of serious adverse events until 30 days after last study treatment administration
- Incidence of progressive disease during neoadjuvant treatment O progressive disease: defined as 20% increase *FTV or >20% increase measured in the longest diameter on DCE-MRI or unequivocal new lesions on (18)F-FDG PET
- Incidence of dose reductions and treatment discontinuations
- Radiologic complete response defined as the absence of pathologic enhancement on contrast enhanced MRI breast
- Pathological complete response (ypT0/is N0) at surgery in patients treated without chemotherapy, and overall
- Residual Cancer burden (RCB, 0-III) at surgery in patients treated without chemotherapy, and overall
- Event-free survival (EFS) defined as the interval from registration to disease progression resulting in inoperability, recurrence, or death from any cause, whichever comes first at 3, 5 and 10 years after registration

- Overall survival (OS) defined as the time from registration to death from any

cause at 3, 5 and 10 years after registration

Study description

Background summary

Breast cancer can be classified into four different types based on the treatment options: hormone sensitive and HER2-negative, hormone sensitive and HER2-positive, hormone insensitive and HER2-positive, and hormone insensitive and HER2-negative. This study concerns exclusively HER2-positive (hormone sensitive or insensitive) breast cancer. HER2-positive breast cancer is characterized by many HER2 on the cancer cells. As a result, cancer cells get a lot of signals to grow and to divide. With this type of breast cancer patients are eligible for targeted therapy, which uses agents that specifically target the HER2 protein. Examples of such targeted medicines are trastuzumab and pertuzumab. Since the advent of these medicines, patient*s outcomes have been improved dramatically. In addition, they give less frequently and less dangerous side effects compared to chemotherapy because they mainly target tumor cells (instead of chemotherapy). However, targeted therapy is nowadays still combined with chemotherapy. Previous studies have shown that some patients can be treated with a chemotherapy-free regimen consisting of solely targeted therapy (with trastuzumab and pertuzumab). However, this applies to a minority of patients.

Tucatinib is a relatively new medicine that also targets HER2. Tucatinib is already being used to treat patients with metastatic breast cancer, and has shown to be effective. Just like trastuzumab and pertuzumab, one of the benefits of tucatinib is that it leads to less frequent and less dangerous side effects compared to chemotherapy. In addition, previous studies have demonstrated that tucatinib also leads to good results in patients with brain metastasis, which until now remains an unmet medical need in HER2+ breast cancer. By combining tucatinib with trastuzumab and pertuzumab and by selecting patients who are likely to have a high chance of response to the targeted therapy, we aim to treat even more patients successfully with a chemotherapy-free regimen. Since it is known that chemotherapy causes many adverse side effects on both the short term and the long term, this new treatment would be a great improvement in the treatment of HER2-positive breast cancer.

Study objective

This study has been transitioned to CTIS with ID 2024-518192-61-00 check the CTIS register

for the current data.

To evaluate safety and feasibility of neoadjuvant chemotherapy-free regimen with trastuzumab, pertuzumab and tucatinib in stage II-III HER2-positive breast cancer.

Study design

TRAIN-4 is a non-randomized, non-comparative, single-center phase 1b study.

All subjects start with three cycles of trastuzumab, pertzumab and tucatinib. One cycle takes three weeks. Trastuzumab and pertuzumab are administered intravenously on day 1 of every cycle, whereas tucatinib is administered orally on daily basis. During treatment in the TRAIN4-study, an MRI scan of the breast is performed every three cycles. If the tumor volume has decreased sufficiently after the third cycle, treatment with trastuzumab plus pertuzumab plus tucatinib will be continued for six more cycles. However, if the tumor volume has not decreased sufficiently, the administration of tucatinib will stop and chemotherapy will be added to the treatment, creating the scheme of paclitaxel, trastuzumab, carboplatin and pertuzumab (PTC-Ptz). Chemotherapy with PTC-Ptz is nowadays standard-of-care for patients with HER2-positive breast cancer.

After completion of neoadjuvant treatment subjects will be operated. After surgery patients will be treated according to national guidelines, for instance with chemotherapy, radiation therapy or hormonal therapy.

Intervention

This study has no intervention or control group. Patients will be treated according to the above mentioned scheme (see *Study design*).

Study burden and risks

Burden
Due to extra checks/investigations subjects need to visit the hospital more frequently than when they get standard-of-care:
- During the first three cycles weekly (including medical check by the investigating doctor and laboratory assessments), cycle 4-9 once every three weeks. In case a patients switches to chemotherapy with PTC-Ptz after three cycles, laboratory investigations are conducted according to the local treatment protocol.
- Two times more often a MRI scan of the breast.
- One time more often a PET scan.
- Two times (at screening and after three cycles) some extra blood (20ml in total, EDTA tubes) will be taken for ctDNA analysis.
- Three more extra biopsies at screening for translational research.

Risks
Trastuzumab, pertuzumab and chemotherapy with PTC-Ptz are already registered as neoadjuvant treatment of HER2-positive breast cancer and considered standard of care. However, tucatinib is no standard treatment yet. The most important side effects of tucatinib are diarrhea, stomatitis, hepatotoxicity, skin rash and nosebleeds. Because of the increased chance of developing diarrhea, subjects will be prescribed loperamide. In addition, subjects will be monitored more frequently than standard-of-care.

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. Signed written informed consent
2. Histologically confirmed primary invasive breast cancer

3. Stage II - IIIA primary breast cancer according to TNM-staging (8th edition, AJCC); (largest tumor diameter DCE-MRI >= 2cm (cT2-3) and/or cN1-2 confirmed with FNA or histology)
4. HER2 overexpression defined as circumferential membrane staining that is complete, intense and in >10% of invasive tumor cells (IHC 3+) on pre-treatment biopsy
5. Known estrogen- and progesterone-receptor expression of the invasive tumor
a. ER-negative or PR-negative is defined as <10% of invasive tumor cell nuclei are immunoreactive in the presence of evidence that the sample can express ER and/or PR
6. WHO performance status 0-1 7. Age (>= 18 years of age)
7. LVEF >=50% measured by echocardiography or MUGA
8. Eligible for neoadjuvant treatment
9. Laboratory requirements within 21 days prior to enrollment: a. Adequate bone marrow function (ANC >=1.5 x 109/l, platelets >=100 x 109/l); b. Adequate hepatic function (ALAT, ASAT and bilirubin <=2.5 times upper limit of normal). Subjects with Gilbert's syndrome may have a total bilirubin >=2.5 × the ULN range, if no evidence of biliary obstruction exists; c. Adequate renal function: creatinine clearance >50 ml/min estimated using the Cockcroft-Gault equation or MDRD equation, or based on a 24-hour urine collection measurement

Exclusion criteria

1. Current pregnancy or breastfeeding
2. Current or previous other malignancy unless treated without systemic therapy and more than five years ago
3. Psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule
4. Use of a strong CYP3A4 or CYP2C8 inhibitor within five half-lives of the inhibitor, or used a strong CYP3A4 or CYP2C8 inducer within five days prior to first dose of study treatment
5. Known chronic liver disease
6. History of inflammatory bowel disease or bowel resection
7. Contraindications for MRI
8. Inflammatory breast cancer, cT4 and/or cN3 tumors
9. Occult breast cancer (cT0)
10. Bilateral breast cancer

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	28-12-2023
Enrollment:	30
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Herceptin
Generic name:	Trastuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Perjeta
Generic name:	Pertuzumab
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Tukysa
Generic name:	Tucatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	20-09-2023
Application type:	First submission
Review commission:	METC NedMec

Approved WMO Date:	15-11-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	02-09-2024
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	17-09-2024
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	CTIS2024-518192-61-00
EudraCT	EUCTR2022-002784-29-NL
CCMO	NL81763.041.22