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Chapter 8

Neoadjuvant trastuzumab, pertuzumab and tucatinib without chemotherapy in stage II-III HER2-positive breast cancer: study protocol for the phase 1b TRAIN-4 study

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In preparation

ABSTRACT

Background

A subset of patients with stage II-III HER2-positive breast cancer can be treated with HER2-blockade alone. The proportion of patients whom can successfully be treated without chemotherapy could potentially be increased by selecting great responders using DCE-MRI and by adding tucatinib to trastuzumab and pertuzumab alone. The aim of this study is to evaluate the safety and efficacy of neoadjuvant treatment with tucatinib, trastuzumab and pertuzumab.

Methods

The TRAIN-4 study is an investigator-initiated, single-center, non-randomized, non-comparative phase 1b study in patients with stage II-III HER2-positive breast cancer and 3+ on immunohistochemistry. All patients will start neoadjuvant treatment consisting of trastuzumab, pertuzumab and tucatinib. Response monitoring takes place after three cycles using MRI. In case of functional tumor volume decrease of at least 65% (responders), patients will continue for six more cycles. However, if functional tumor volume reduction is less than 65% (non-responders), patients will switch to receive six cycles paclitaxel, carboplatin, trastuzumab and pertuzumab. The primary endpoint is incidence and severity of all grade adverse events until 30 days after last study treatment administration and will be evaluated by the safety committee. Feasibility, defined as the proportion of patients without disease progression until surgery, is a main secondary study parameter. The study will not be considered feasible if four or more patients have disease progression. An interim analysis for safety and feasibility will be performed after 15 patients. Furthermore, the feasibility and accuracy of functional tumor volume decrease on DCE-MRI scan and SUVmax decrease on (18)F-FDG PET scan to predict pCR after three, six or nine cycles will be assessed by calculating the negative predictive value, positive predictive value, sensitivity and specificity.

Discussion

The TRAIN-4 study design investigates a new strategy to increase the number stage II-III HER2-positive breast cancer patients that can be treated completely without chemotherapy. The study will possibly prevent more patients from toxicity by chemotherapy and hopefully prevent more CNS metastasis. Since patients undergo both FDG-PET and MRI, the best imaging modality can be selected to progress to a larger efficacy trial.

Trial registration

EudraCT-number: 2022-002784-29 (10 May 2023); ClinicalTrials.gov Identifier: NCT06162559

BACKGROUND

The treatment of early human epidermal growth factor receptor 2 (HER2)-positive breast cancer evolved drastically since the introduction of the HER2-directed monoclonal antibodies trastuzumab and pertuzumab. Pathological complete response (pCR) rates up to 60-70% overall and 80-90% in hormone receptor (HR)-negative patients have been reported [1-3]. Reaching a pCR after neoadjuvant chemotherapy is a good predictor for survival in HER2-positive breast cancer and can therefore be used as a surrogate endpoint in clinical trials [4-10]. Three-year event-free survival (EFS) rates of patients treated with dual HER2-blockade in combination with chemotherapy range between 84-94% with corresponding three-year overall survival (OS) between 93-98% [6,8,11].

Chemotherapy-free regimens

These outcomes for HER2-positive, early-stage breast cancer patients are the inspiration for multiple chemotherapy de-escalation studies. For instance, patients with stage I-II lymph node negative disease showed excellent results when treated with only trastuzumab and paclitaxel [12,13]. In our institute, we recently investigated image-guided chemotherapy de-escalation based on radiologic complete response on Dynamic Contrast Enhanced (DCE) MRI in the TRAIN-3 trial (NCT03820063; PD18-06). Recently, several other trials demonstrated that in an important subset of patients a pCR can be reached with HER2 blockade alone (*Table 1*) with pCR rates ranging from 11% after one cycle of trastuzumab and lapatinib up to 45% in HR-negative/HER2-positive early responders in the WSG-TP-II treated with 12 weeks trastuzumab and pertuzumab [1,14-18]. The results of PHERGAIN showed that ^{18}F-FDG PET could be a useful strategy to select appropriate candidates who can be treated without chemotherapy [19]. The pCR rate was 38% in PET-responders after eight cycles of trastuzumab and pertuzumab and an impressive 98.8% 3-year invasive disease-free survival in the group treated without chemotherapy. These patients can thus be spared the side effects of chemotherapy. Overall, the highest efficacy of chemotherapy-free treatment is seen in patients with HER2 immunohistochemistry (IHC) 3+ tumors [16,17,19,20]. Further improvement of pCR rates using new anti-HER2 agents and improved patient selection using predictive biomarkers are required to bring chemotherapy-free approaches to the clinic.

Table 1. Overview of trials including patients with HER2-positive breast cancer treated without neoadjuvant chemotherapy.

Trial	Treatment		pCR (ypT0/is, N0) (%)	PD (%)
EPHOS-B	1 x T + Lap		11%*	*
NeoSphere	4 x T + Ptz		11%*	6%**
TBCRC026	4 x T + Ptz		34%*	8%**
TBCRC006	12 x T + Lap	HR-negative	28%	3%
	12 x T + Lap + ET	HR-positive	18%	
PHERGAIN	8 x T+ Ptz + ET	PET-responders***	38%*	2%**
WSG-TP-II	4 x T+ Ptz + ET	HR-positive	24%	
	4 x T + Ptz	HR-negative	34%	
		HR-negative, early responders	45%****	
PAMELA	6 x T + Lap		35%	

*ypT0/is (no axillary staging known)
** defined as surgery not as planned due to insufficient response
*** ≥40% ΔSUVmax on FDG-PET after two cycles
**** ≥30% Ki-67 decrease or <500 invasive tumor cells in biopsy after one cycle
PD = progressive disease, T = trastuzumab, Ptz = pertuzumab, Lap = lapatinib, ET = endocrine treatment.

Tucatinib

The highly selective anti-HER2 tyrosine kinase inhibitor tucatinib has shown to be effective and well tolerated when added to trastuzumab and capecitabine in advanced HER2-positive breast cancer [21]. Importantly, tucatinib is so far the first tyrosine kinase inhibitor to show improved outcomes for CNS events and may help to prevent CNS recurrences [22]. Given the high activity in advanced HER2-positive breast cancer, tucatinib holds great promise in the early breast cancer setting. In the I-SPY2-trial, tucatinib added to trastuzumab, pertuzumab and paclitaxel showed promising activity with 89% of patients reaching >80% functional tumor volume decrease after 12 weeks [23]. In the safety run-in of the I-SPY2 trial, 7 of 20 patients (35%) developed reversible grade ≥3 AST/ALT elevation [23]. This is probably due to the combination of paclitaxel and tucatinib, since tucatinib is a strong CYP3A4 and weak CYP2C8 inhibitor and paclitaxel is metabolized by CYP3A4 and CYP2C8. Previously, liver test abnormalities were found with the combination of lapatinib and paclitaxel, although in lower grades and incidence [24]. Since the data of I-SPY2 demand caution, a safety study evaluating this new combination should prelude a larger clinical trial.

Image-guided treatment

An early radiologic (complete) response on MRI breast is a good predictor for pCR and long-term outcomes, but accuracy differs between breast cancer subgroups [25-27]. The negative predictive value (NPV; pCR in case of rCR) in HER2+/HR- patients ranges from 69-88% versus 42-78% in HER2+/HR+ patients [25,28-32]. To identify patients with an early response to neoadjuvant treatment, volume metric features assessed by MRI have shown to be more

predictive than two-dimensional measurements [33-35]. A recently presented small study (n=49) within the I-SPY2 consortium found that a decrease in FTV of at least 65% after 6 weeks corresponds with a NPV of 79% and positive predictive value (PPV) of 80% for RCB 0 or 1 across breast cancer subtypes [36]. However, this study was performed in patients treated with chemotherapy. Therefore, we hypothesize that a 65% decrease in FTV on MRI after 9 weeks in patients treated with a chemotherapy-free regimen could safely select chemotherapy-free treatment candidates.

The predictive value of an early metabolic response is investigated in PHERGAIN, TBCRC026, NeoALLTO and PREDIX HER2 [19,26,37,38]. TBCR026 found that a decrease in SULmax of greater than or equal to 40% after 15 days of trastuzumab plus pertuzumab corresponds with a NPV of 88% for pCR [15]. However, PPV was only 49%. They used the SULmax to correct the SUVmax for lean body mass. In PHERGAIN, patients underwent an ^{18}F-FDG PET after two cycles [19]. They defined responders as 40% decrease in SUVmax uptake and found a pCR rate of 38% in responders [19]. In PREDIX HER2 they used a threshold of ΔSUVmax ≥68.7%, leading to a pCR rate of 57.4% in responders after two cycles [38]. In the NeoALLTO trial a pCR rate of 43.6% in the breast was found among patients with at least 25% decrease in SUVmax after two cycles, but only 23.5% within HR-positive responders, which is not sufficient for chemotherapy de-escalation [26].

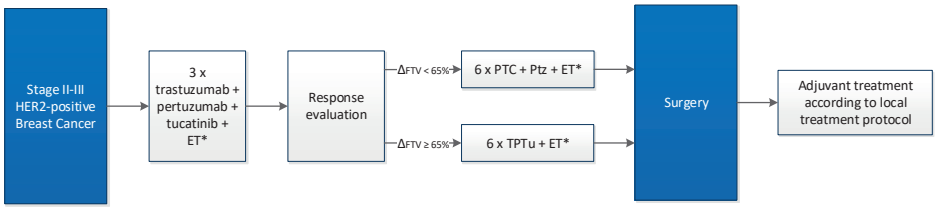
Overall, functional tumor volume decrease of 65% or more on DCE-MRI as used in the I-SPY2 is the modality with the highest predictive value for response evaluation of neoadjuvant treatment for HER2-positive breast cancer patients. SUVmax and SULmax measurements with ^{18}F-FDG PET will help to compare outcomes to other studies and optimize response prediction algorithms for future studies.

In summary, previous studies have shown that a subset of patients with early stage HER2-positive breast cancer can be treated with HER2-blockade alone. By adding tucatinib to standard targeted therapy with trastuzumab and pertuzumab AND by selecting appropriate candidates using DCE-MRI, we hypothesize that even more patients can be successfully treated without chemotherapy. The aim of this study is to evaluate the safety and initial efficacy of neoadjuvant treatment with tucatinib, trastuzumab and pertuzumab. If safe, a larger comparative study will follow to compare this regimen to standard-of-care neoadjuvant treatment. Biomarker analyses in the TRAIN-4 will help to select appropriate candidates for the comparative trial.

METHODS/DESIGN

The TRAIN-4 study is an investigator-initiated, single-center, non-randomized, non-comparative phase 1b study in patients with stage II and III HER2-positive breast cancer. All patients will start neoadjuvant treatment consisting of trastuzumab, pertuzumab and tucatinib. Patients with hormone receptor positive disease will receive concurrent endocrine therapy using an aromatase inhibitor, combined with an LHRH-agonist if pre-menopausal. Response monitoring will be performed after three cycles using contrast-enhanced breast MRI. In case of functional tumor volume decrease of at least 65%, patients will continue treatment for six more cycles. However, if functional tumor volume reduction is less than 65%, patients will switch to receive six cycles paclitaxel, carboplatin, trastuzumab and pertuzumab. After completion of neoadjuvant systemic treatment, patients will undergo surgery and receive adjuvant treatment according to the local treatment protocol.

A schematic overview of the study design is shown in *Figure 1*.



Primary endpoint:
all grade AEs

Key Secondary endpoints:
pCR, rCR, disease progression
Dose reductions, treatment discontinuations
EFS, OS

Response evaluation: DCE-MRI breast, 18(F)FDG-PET, and liquid biopsy.
Response after 3 cycles is defined by at least 65% reduction in functional tumor volume (FTV) on MRI

*Patients with endocrine sensitive disease receive concurrent endocrine therapy (ET) with an aromatase inhibitor
T= trastuzumab, P= paclitaxel, C = carboplatin, Ptz = pertuzumab, Tu = tucatinib

Inclusion criteria

Eligible patients are 18 years or older, have good performance status (WHO 0 or 1) and have histologically confirmed stage II-IIIA primary invasive breast cancer with HER2 overexpression (defined as circumferential membrane staining that is complete, intense and in more than 10% of the invasive tumor cells (IHC 3+)). Tumors can be estrogen and/or progesterone positive (ER/PR ≥10%) or negative. Patients have a left ventricular ejection fraction (LVEF) of 50% or higher measured by echocardiography or MUGA, absolute neutrophil count ≥1.5 x 10^9/l, platelets ≥100 x 10^9/l, ALAT, ASAT and bilirubin ≤2.5 times upper limit of normal, and a creatinine clearance >50 ml/min (estimated using the Cockroft

Gault equation or MDRD equation, or based on a 24-hour urine collection measurement). The patient must be able and willing to give informed consent.

Exclusion criteria

Patients are excluded from this study in case of occult breast cancer (cT0/cTis), inflammatory breast cancer, a breast tumor with direct extension to the chest wall or to the skin (cT4) and in case of metastasis in infraclavicular lymph node(s), ipsilateral internal mammary lymph node(s) in the presence of axillary lymph node metastasis or metastasis in ipsilateral supraclavicular lymph node(s) (cN3). Patients with current or previous other malignancies unless treated without any systemic therapy and more than five years ago are also not eligible for study participation. Other exclusion criteria include current pregnancy of breastfeeding, psychological, familial, sociological, or geographical condition potentially hampering compliance with the study protocol and follow-up schedule, 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, chronic liver disease, history of inflammatory bowel disease or bowel resection, and any contraindications for MRI.

Objectives

The primary objective of the study is to evaluate the safety of neoadjuvant trastuzumab, pertuzumab and tucatinib. The primary endpoint is incidence and severity of all grade adverse events until 30 days after last study treatment administration, which will be described according to CTCAE 5.0. The steering committee of this study will function as safety committee and will declare if this new treatment combination is safe.

Secondary safety endpoints include incidence of serious adverse events and incidence of dose reductions and treatment discontinuations. Another secondary endpoint is feasibility, which is defined as the proportion of patients without disease progression until surgery. Efficacy needs to be assessed in a larger phase 2 or 3 trial but will also be determined in this study. Secondary efficacy endpoints include radiologic complete response (rCR), pathological complete response (pCR), residual cancer burden (RCB, 0-III) at surgery and event-free survival (EFS) and overall survival (OS) at 3, 5 and 10 years after registration. We will evaluate the accuracy of two imaging techniques (DCE-MRI and FDG-PET) to predict pCR. In addition, we will conduct biomarker analyses, involving baseline and on-treatment tumor biopsies and liquid biopsies, to explore biomarkers that could identify subgroups of patients who can be treated without chemotherapy.

Interventions

All patients will start neoadjuvant treatment with three cycles of trastuzumab, pertuzumab and tucatinib. Trastuzumab (loading dose 8 mg/kg; subsequent doses 6 mg/kg) and pertuzumab (loading dose 840 mg; subsequent doses 420 mg) will be administered

intravenously on the first day of each cycle. Tucatinib (300 mg) will be taken orally twice-daily on day 1-21. Tucatinib will be provided by Seagen Inc. Patients with hormone receptor positive disease will also receive endocrine therapy with an aromatase-inhibitor. In addition, premenopausal women are concurrently treated with an LHRH-agonist.

After three cycles, response monitoring will be performed using DCE-MRI. In case of functional tumor volume decrease of at least 65% (responders), patients will continue treatment for six more cycles of the chemotherapy-free regimen. If tumor response is <65% (non-responders), patients will switch to receive six cycles paclitaxel, carboplatin, trastuzumab and pertuzumab. After completion of neoadjuvant systemic treatment, patients will undergo surgery within 6 weeks and receive adjuvant treatment according to the local treatment protocol.

Dose modifications

In case of significant treatment-related toxicity, dose modification of tucatinib may be required. The dose will be adjusted depending on the nature and severity of the adverse events. Treatment interruption of tucatinib may be required. Dose adjustment is not permitted for trastuzumab, pertuzumab, however treatment interruption could be required. Treatment with endocrine therapy will continue in case of treatment interruption of tucatinib and/or trastuzumab, and or pertuzumab. Details about dose modifications can be found in additional file 1: dose modifications.

Concomitant treatment

Patients will be instructed to discuss all concomitant medications before taking them with their treating physician. Concomitant anti-cancer or investigational treatment that is not per-protocol is not allowed during the study period. Other medications not allowed during study participation include growth factors (including G-CSF), strong CYP3A4 inducers and strong CYP2C8 inhibitors or inducers. Supportive treatment with anti-emetics is allowed. Chemotherapy in non-responders with co-medication and anti-emetics follows local chemotherapy guidelines. Alternative endocrine options (e.g. exemestane or tamoxifen) are allowed in case of intolerance to the prescribed (per-protocol) aromatase-inhibitors or LHRH-agonists. Local treatment after completion of neoadjuvant chemotherapy consists of surgery with or without radiation therapy, depending on recommendations by the local multidisciplinary tumor board. Local regional treatment may be performed early in case of unacceptable toxicity or progressive disease after consulting the primary investigator and in the latter case local treatment may or may not include surgery depending on operability of the tumor.

Participant timeline

A table of all study-related visits and interventions can be found in additional file 2: Summary table of study activities.

Statistical considerations: Sample size and power

This phase 1b study is of descriptive nature to evaluate safety and feasibility of a chemotherapy-free regimen with trastuzumab, pertuzumab and tucatinib. The sample size is comparable to the initial tucatinib plus capecitabine and trastuzumab (n=27) cohort in a phase 1b study and has no formal statistical basis. A sample size of 30 patients (15 per HR-subgroup) is considered sufficient for safety analysis.

Statistics: Analysis

All patients who receive at least one cycle of study treatment will be included in the intention-to-treat population for analysis for the primary safety analysis. The study population will be divided in responders (ΔFTV ≥65%) and non-responders (ΔFTV <65%).

Primary study parameter

The primary endpoint is incidence and severity of all grade adverse events (AEs) until 30 days after last study treatment administration. The expected overall grade ≥3 AEs is between 20% and 50% based on the combination with capecitabine and trastuzumab [39]. The percentage of patients experiencing toxicities will be reported separately for responders (i.e. treated without chemotherapy) and non-responders (i.e. treated with chemotherapy).

During this study, the steering committee will function as safety committee and will evaluate safety of the combination of trastuzumab, pertuzumab and tucatinib and the image-guided de-escalation method used in this study. Data from the TRAIN-2 study showed that 98/219 (44.7%) experienced non-hematological grade ≥3 toxicities. After 15 patients, the percentage of patients who had non-hematological grade ≥3 toxicities will be calculated, with a one-sided 90% confidence interval. If the 90% TRAIN4-confidence interval falls above the upper limit of the TRAIN2-confidence interval (0.38-0.516), the study will be closed early due to overwhelming toxicity.

Secondary study parameters

One of the main secondary study parameters is feasibility. Feasibility of this study is defined as the proportion of patients without disease progression until surgery. The study will not be considered feasible if more than 10% of patients have disease progression before surgery (corresponding with ≥4 of 30 patients). Moreover, the trial must stop early if two or more out of the first 15 patients have documented disease progression before surgery.

Furthermore, the feasibility and accuracy of functional tumor volume decrease on DCE-MRI scan and SUVmax decrease on (18)F-FDG PET scan to predict pCR after three, six or nine cycles will be assessed by constructing 2x2 tables and calculating the negative predictive value (NPV), positive predictive value (PPV), sensitivity and specificity. Other secondary endpoints including serious adverse events, frequency of dose reductions and treatment discontinuations, residual cancer burden, and 3-, 5- and 10-year EFS and OS

(which will be estimated by the Kaplan Meier method) will be reported for responders and non-responders.

The TRAIN-4 study will not be powered for identifying subgroups, but will explore feasible and interesting translational research subjects to identify biomarkers to asses in the phase 2/3 clinical trial.

Ethics and logistics

The TRAIN-4 study was approved by the accredited Medical Ethics Research Committee (MREC) NedMec on September 20th, 2023. The study will be conducted in agreement with either the Declaration of Helsinki and the laws and regulations of the Netherlands (WMO), whichever provides the greatest protection of the patient. The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice.

All data will be recorded by qualified data managers in an electronic case report form (eCRF) developed in ALEA® by the data center of the NKI-AvL. Data monitoring will be performed by the appointed monitor according to the guideline 'Kwaliteitsborging Mensgebonden Onderzoek' of the Netherlands Federation of University Medical Centres (NFU).

DISCUSSION

The TRAIN-4 study will evaluate neoadjuvant trastuzumab, pertuzumab and tucatinib as a chemotherapy-free regimen for stage II and III HER2-positive breast cancer patients by assessing safety, estimating initial efficacy and evaluating the accuracy of FTV decrease on DCE-MRI to predict pCR. A chemotherapy-free start of treatment has been investigated in multiple clinical trials and have shown a low rate of disease progression in the chemotherapy-free arms leading to inoperability, ranging between 0 and 8% [1,15,18,19]. Moreover, the combination of tucatinib, trastuzumab and pertuzumab is hypothesized to be more potent than the combination of only two HER2-directed agents. Furthermore, in the TRAIN-4 study we will select patients with IHC 3+ disease to increase the upfront probability of a complete response after HER2-targeting therapy without chemotherapy. The FTV decrease threshold is chosen to minimize the risk for patients to need additive cytotoxic treatment in the case of initial great response. The TRAIN-4 approach aims to increase the proportion of stage II-III HER2-positive breast cancer patients eligible for chemotherapy-free treatment to potentially spare them from chemotherapy-related side effects and thereby increase health-related quality of life. If the study is declared not feasible based on the earlier mentioned pre-set boundaries, a follow-up study should amend its design in terms of treatment regimen, selection criteria or response monitoring.

Trial status: recruiting started in December 2023.

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