A phase III prospective, two-cohort non-randomized, multi-centre, multinational, open label study to assess the safety of assisted- and self-administered subcutaneous trastuzumab as therapy in patients with operable Her2-positive early breast cancer.

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

Summary

ID

NL-OMON43630

Source
ToetsingOnline

Brief title
SafeHer Study

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
breast cancer, HER-2 positive breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: Roche Nederland B.V.
Source(s) of monetary or material Support: Roche Nederland B.V.

Intervention

Keyword: Breast cancer, HER2, Subcutaneous, Trastuzumab

Outcome measures

Primary outcome

The primary study parameters are all clinical adverse events (AEs) and serious adverse events (SAEs) as well as laboratory abnormalities will be recorded and graded according to the NCI-CTCAE version 4.0.

Cardiac function will be evaluated by measuring LVEF by echocardiography, MUGA scan or MRI and ECG.

Secondary outcome

Efficacy is measured by the following parameters:

- disease-free survival (DFS)

- overall survival (OS)

Patient satisfaction with trastuzumab SC administration using the SID.

Study description

Background summary

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide. Studies have shown that women whose tumours exhibit either amplification of the HER2 gene or overexpression of its encoded protein have a more aggressive form of breast cancer that is associated with

significantly shortened disease-free (DFS) and overall survival (OS) compared with women whose tumours do not over express HER2. Trastuzumab (Herceptin) is a humanized monoclonal antibody directed against the extracellular domain of HER2. It is indicated for the treatment of patients with HER2-positive MBC and EBC and HER2-positive metastatic gastric cancer. The efficacy and safety of intravenous (IV) trastuzumab have been well characterized. Subcutaneous administration of trastuzumab takes significantly less time (up to 5 minutes) compared to IV infusion (30 to 90 minutes) and this is expected to improve treatment convenience and compliance.

Study objective

The main purpose of this study is to determine the side effects of trastuzumab when it is given by each of these subcutaneous injection methods. The study will also gather information about whether and when the cancer comes back after taking trastuzumab in this way and also how the patient feel using the device to give trastuzumab to themself (if the patient should receive it).

Study design

One subcutaneous injection method looked at in this study uses a standard needle used for injections under the skin with a separate syringe (a tube with a plunger inside). The study doctor or nurse fills the syringe with trastuzumab, attaches the needle to it, and then gives the drug through the skin. The injection takes up to 5 minutes.
The other method uses a device that has a needle and trastuzumab already in it. The device is placed on the skin. When a button is pressed, the needle passes into the skin and the trastuzumab is delivered under the skin. This injection also takes up to 5 minutes. After being shown how to use this device, people can give trastuzumab to themselves without needing a doctor or nurse to help, but with
one of them being present. Each device, called single use injection device, should be used only once. The study doctor will decide which group the subject will be in. The whole study will take around 8 years to complete. Your participation in the study will include 1 year of treatment and up to 5 years of follow-up. However, the time you are followed after completing treatment may be shorter. Also, the study may be terminated earlier than 5 years in case of major safety concerns or other reasons.

Intervention

Trastuzumab subcutaneous 600 mg in 5 mL.

Study burden and risks

Study screening period procedures include: * Pregnancy blood test if the

subject is a woman who is able to have children. This test must be done within 7 days before the first trastuzumab study treatment. If the blood test has been done between 14 and 7 days before the first study treatment, a urine pregnancy test will be done within 7 days of the first treatment (instead of another blood test) * Electrocardiogram (ECG) * During study treatment period the subjects will receive 1 trastuzumab treatment every 3 weeks for a total of 18 treatments (about 12 months) unless they experience unacceptable side effects or their cancer comes back (in which case the study treatment would be stopped).

During study treatment: * Recording of the blood pressure (while you are sitting) and heart rate before and after some of the study treatments (1st, 5th, 9th, 13th, and 18th treatment; about every 3 months) * Questionnaire about the device. If the subjects were assigned to receive trastuzumab using the device that allows they to give the injection themself, after they have received the 4th study treatment they will be asked to complete a questionnaire about what they thought about the device * ECG before every fourth trastuzumab treatment (about every 3 months) * Pregnancy blood test if, at any time, it appears that the subject may be pregnant.

Study follow-up period procedures include: * Questionnaire about the device. If the subjects were assigned to receive trastuzumab using the device that allows them to give the injection themself, within 4 weeks of their last study treatment they will be asked to complete a questionnaire about what they thought about the device * Recording of the blood pressure (while you are sitting) and heart rate 4 weeks after the last study trastuzumab treatment * Blood collection (about 2 tablespoons) for laboratory tests of the overall health 4 weeks after the last study trastuzumab treatment * ECG 4 weeks and at 6, 12 and 24 months after the last study trastuzumab treatment * ECHO, MUGA, or MRI 4 weeks and at 6, 12 and 24 months after the last study trastuzumab treatment * Any physical signs or symptoms suggesting that the heart is not working properly will be recorded 4 weeks and at 6, 12 and 24 months after the last study trastuzumab treatment * Regular follow-up (about every 6 months) to check whether the cancer has come back. This may include physical exams, mammography (breast x-ray) and pelvic exams as determined by the study doctor. The study doctor will explain what the cancer follow-up procedures will be * Pregnancy blood test any time for at least 6 months after the trastuzumab treatment, if it appears that the subject may be pregnant.

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 approved by the reviewing independent Ethics Committee;2. Female or male aged 18 years or above;3. Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1;4. Histologically confirmed early invasive HER2-positive carcinoma of the breast with no evidence of residual, locally recurrent or metastatic disease and defined as clinical stage I (T1, N0, M0) to IIIC (any T, N3, M0) that is eligible for adjuvant treatment with trastuzumab.;Note: Patients treated without neoadjuvant or adjuvant chemotherapy, such as patients with low risk node negative tumours * 1.0 cm, elderly patients (>65 years of age) or patients with HER2-positive EBC but denying chemotherapy, will also be eligible to participate in the study, but their enrolment will be limited to approximately 10% of the total study population.;5. HER2-positive EBC, defined as IHC 3+, or a positive in situ hybridization (ISH testing) by validated and approved methods within a certified laboratory;6. Screening left ventricular ejection fraction (LVEF) * 55% as measured by echocardiography, Multi Gated Acquisition (MUGA) scan or Magnetic Resonance Imaging (MRI) per local practice.;7. Agreement to use an adequate, non-hormonal means of contraception by women of childbearing potential (defined as pre-menopausal and not surgically sterilized or <1 year after the onset of menopause) and by male participants with partners of childbearing potential only. Examples of adequate contraceptive measures are an intra-uterine device, a barrier method (condoms, diaphragm) in conjunction with spermicidal

jelly, or total abstinence. Oral, injectable, or implant hormonal contraceptives are not acceptable for females participating in the study.;8. Intact skin at site of SC injection on the thigh.

Exclusion criteria

Cancer Related Criteria;1. Previous neoadjuvant or adjuvant breast cancer treatment with an approved or investigational anti-HER2 agent;2. History of other malignancy which could affect compliance with the protocol or interpretation of results (including previous invasive ipsilateral or contralateral breast cancer). Patients with curatively treated carcinoma in situ of the cervix or basal cell carcinoma, and patients with other curatively-treated malignancies, other than breast cancer, who have been disease-free for at least 5 years, are eligible.;3. Past history of ductal carcinoma in situ (DCIS) within the last 5 years that has been treated with any systemic therapy OR with radiation therapy to the ipsilateral breast where invasive cancer subsequently develops. Patients who had their DCIS treated with surgery only are allowed to enter the study.;4. Metastatic disease;Haematological, Biochemical and Organ Function Related Criteria;5. Inadequate bone marrow function (as indicated by any of the following):;* Total white blood cell count < 2,500 / mm3 (<2.5 x 109/L);*Neutrophil count <1,500 / mm3 (<1.5 x 109/L);* Platelets <100,000 / mm3 (<100 x 109/L);* Haemoglobin <10 g/dL;6. Impaired hepatic function (as indicated by any of the following):;* Serum total bilirubin >1.5 x upper limit of normal (ULN);* Alanine amino transferase > 2.5 x ULN
* Aspartate amino transferase > 2.5 x ULN;* Alkaline phosphatase >2.5 x ULN;7. Impaired renal function: serum creatinine >1.5 x ULN;Other Study Drug Related Exclusion Criteria;8. Serious cardiac illness or medical conditions including but not confined to:;* History of documented heart failure or systolic dysfunction (LVEF <50%);* High-risk uncontrolled arrhythmias such as atrial tachycardia with a heart rate >100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade atrioventricular (AV) block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block);* Angina pectoris requiring anti-anginal medication;* Clinically significant valvular heart disease;* Evidence of transmural infarction on electrocardiogram (ECG);* Poorly controlled or uncontrolled hypertension (blood pressure constantly over 140/90 mm/hg, despite treatment), or history of hypertensive crisis or hypertensive encephalopathy
9. Other concurrent serious diseases that may interfere with planned treatment including severe pulmonary conditions/illness;10. Prior maximum cumulative dose of doxorubicin >360 mg/m2 or maximum cumulative dose of epirubicin >720 mg/m2 or equivalent;11. Known hypersensitivity to trastuzumab, murine proteins, or excipients, or a general hypersensitivity to adhesives (Cohort B only);12. History of severe allergic or immunological reactions, e.g. difficult to control asthma;General Exclusion Criteria;13. Pregnancy or lactation;14. Unable or unwilling to comply with the requirements of the protocol as assessed by the investigator;15. Concurrent enrolment in another clinical trial using an investigational anti-cancer treatment, including hormonal therapy, bisphosphonate therapy and immunotherapy, within 28 days prior to the first dose of study treatment;16. Major surgical procedure or significant traumatic injury within 14 days prior to the first dose of study treatment or anticipated need for major surgery during the course of study treatment except for breast cancer surgery for patient receiving study drug in the neoadjuvant setting. Patients must be free of any clinically

significant sequalae of prior surgery before they can receive their first dose of study treatment.;17. More than 12 weeks between the end of the last chemotherapy cycle and the first dose of study treatment, in case these treatments are initiated sequentially. This criterion does not apply to patients who are starting trastuzumab SC without previous or concurrent chemotherapy or concurrently with chemotherapy.;18. Current peripheral neuropathy of grade 3 or greater per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-09-2012
Enrollment:	80
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Trastuzumab
Generic name:	Herceptin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	05-03-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	25-06-2012
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-07-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-09-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-09-2012
Application type:	Amendment

Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-10-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	09-10-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-10-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-11-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-12-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-12-2012
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-01-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO	

Date:	17-01-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-01-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-04-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	24-06-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	27-06-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	06-01-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United

	(Nieuwegein)
Approved WMO Date:	27-02-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	17-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	14-07-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	03-08-2015
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-11-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-12-2016
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-12-2016

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	04-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	10-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	30-01-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-01-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	11-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	11-12-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2011-005328-17-NL
CCMO	NL39746.060.12