A randomized phase II trial of pertuzumab in combination with trastuzumab with or without chemotherapy, both followed by T-DM1 in case of progression, in patients with HER2-positive metastatic breast cancer

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Primary objectivesThe primary objective of this trial is to evaluate the efficacy in terms of overall survival (OS) at 24 months of a chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line...

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

Summary

ID

NL-OMON44863

Source
ToetsingOnline

Brief title
PERNETTA

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
Breast cancer

Research involving

Human

Sponsors and support

Primary sponsor: UNICANCER
Source(s) of monetary or material Support: SAKK; Swiss Group for Clinical Cancer Research

Intervention

Keyword: Her 2 positive, metastatic breast cancer, pertuzumab, T-DM1

Outcome measures

Primary outcome

Overall Survival at 24 months

Secondary outcome

1) OS at 24 months

2) Progression free survival (PFS) of first-line treatment ignoring first

central nervous system

lesion (CNS) lesion

3) PFS of second-line treatment

4) PFS of second-line treatment ignoring first CNS lesion

5) Time to failure of strategy (TFS) of first- plus second-line treatment

6) OS

7) Objective response (OR) of first-line treatment (based on investigator

assessment)

8) Disease control (DC) of first-line treatment (based on investigator

assessment)

9) OR of second-line treatment (based on investigator assessment)

10) DC of second-line treatment (based on investigator assessment)

11) Adverse events (AEs) according to the NCI CTCAE v4.0 of first-line treatment

12) AEs according to the NCI CTCAE v4.0 of second-line treatment

13) AEs grade *2 until first progression (ignoring first CNS lesion)

14) QoL

15) PFS of third-line treatment

16) Further treatment lines (third-line etc.)

17) Time to CNS metastases

18) Time from first CNS metastases to death

Study description

Background summary

For many physicians the standard of care for Her2 positive metastatic breast cancer is to give chemotherapy in combination with anti-HER2 treatment upfront even though the superiority of this approach compared to a sequential approach adding chemotherapy to trastuzumab only if disease progression occurs, has never been proven. Patients treated with with the combination of chemotherapy and an anti Her2 medicine experience a lot of side effects.
Delaying the use of chemotherapy through the introduction of trastuzumab plus pertuzumab as first-line treatment followed by T-DM1 as second-line treatment, may be equally effective and may be even advantageous for patients in terms of overall survival.
Thus, before considering a phase III trial, data in terms of efficacy and toxicity of both treatment arms should be generated.

Study objective

Primary objectives
The primary objective of this trial is to evaluate the efficacy in terms of overall survival (OS) at 24 months of a chemotherapy-free dual HER2-inbibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) and of a chemotherapy-containing dual HER2-inhibition with trastuzumab and pertuzumab (first-line) followed by T-DM1 (second-line) in patients with HER2- positive metastatic breast cancer.
Secondary objectives:
· To evaluate other efficacy parameter

· To evaluate the safety and tolerability profile of the two treatment strategies
· To evaluate the Quality of Life (QoL)
· To learn how patients are treated after trial treatment

Study design

Multicenter, randomized, open label, phase II trial.

Intervention

First line treatment
Arm A:
* Pertuzumab: 420 mg, every 3 weeks untill first progression. First dose 840 mg.
* Trastuzumab: 6 mg/kg, every 3 weeks untill first progression. First dose 8 mg/kg.
* Patients with hormone receptor positive disease should receive endocrine treatment
Arm B:
* Pertuzumab, trastuzumab
plus
* Paclitaxel: 90 mg/m2 on day 1, 8 en 15; q4w (at least 4 months unless unacceptable toxicity or progressive disease is observed)
or
* Vinorelbine: 25 mg/m2 on day 1 and 8; thereafter 30 mg/m2 on day 1 and 8, q3w (at least 4 months unless unacceptable toxicity or progressive disease is observed)
Patients with hormone receptor positive disease should receive endocrine treatment

Second line treatment
Arm A and arm B:
* T-DM1 (trastuzumab-emtansine): 3,6 mg/kg q3w

Study burden and risks

Similar to treatment of all malignant tumors there is a risk that the drugs used in this trial give adverse events.
Most adverse events will disappear shortly after the tumor treatment, but in rare cases can cause long-term serious complications.
All drugs used in this trial are registered.
Burden: the frequentcy of the visits is the same as standard treatment, only the quality of life questionairs are an extra burden.
(every 3 months max 24 months).

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

- Histologically confirmed breast cancer with distant metastases;Notes :;1. A biopsy from the primary tumor or a metastasis can be used for diagnosis.;2. Patients with non-measurable lesions are eligible.;3. Patients with inoperable, locally advanced breast cancer with lymph node metastases other than ipsilateral locoregional (axillary, infraclavicular, parasternal) or other distant metastases are eligible.;4. Patients with bone metastases with or without bone targeted therapy (bisphosphonates, denosumab) are eligible.;5. Patients with de-novo Stage IV disease are eligible.;- HER2-positive tumor according to central pathology testing for HER2;Note:;1. A formalin-fixed paraffin-embedded (FFPE) biopsy from the primary tumor or a metastasis has to be used for HER2 status determination. If a biopsy is available from a metastasis, the HER2 testing should be performed using the metastasis.;2. Fine needle aspiration is not acceptable for HER 2 testing.;- Women aged *18 years;- WHO performance status 0 to 2 (see Appendix 2);- Left Ventricular Ejection Fraction (LVEF) *50% as determined

by either ECHO or MUGA;- Adequate organ function, evidenced by the following laboratory results:;Neutrophils >1.5x10^9/L, platelets >100x10^9/L, hemoglobin *90g/L, total bilirubin *1.5xULN (unless the patients has documented Gilbert*s disease), AST*3xULN, ALT *3xULN, AP *2.5xULN (except in patients with bone metastases: AP *5xULN), creatinine *1.5xULN;- At least one dose of trial therapy in the first-line treatment phase of this trial;- Proven disease progression on first-line therapy or radiotherapy of a bone metastasis;Notes:;First new parenchymal CNS metastases only do not count as progression requiring the initiation of second line trial treatment (please see Appendix 1.4, Determination and evaluation of new lesions).;Radiotherapy of a single area only for pain control is allowed and will not count as PD.;- Adequate organ function, evidenced by the following laboratory results:;Neutrophils >1.5x10^9/L, platelets >100x10^9/L, hemoglobin *90g/L, total bilirubin *1.5xULN (unless the patients has documented Gilbert*s disease), AST *3xULN, ALT *3xULN, AP *2.5xULN (except in patients with bone metastases: AP *5xULN), creatinine *1.5ULN;- LVEF *50% as determined by either ECHO or MUGA;- QoL questionnaire has been completed.;- Negative serum pregnancy test in women of childbearing potential

Exclusion criteria

- Prior chemotherapy for inoperable locally advanced or metastatic breast cancer;Note:;Prior neoadjuvant/adjuvant chemotherapy is allowed if doses for anthracylines have not exceeded 720mg/m2 and 240mg/m2 for epirubicin and doxorubicin, respectivel.;- Reexposure to paclitaxel is permitted, if the last dose of taxane was given at least 1 year before randomisation.;- Reexposure to vinorelbine is permitted, if the last dose of vinorelbine was given at least 1 year before randomisation.;- Prior anti-HER2 treatment for metastatic or inoperable breast cancer;Note:;Prior neoadjuvant/adjuvant anti-HER2 treatment with trastuzumab and/or lapatinib is allowed.;- More than one endocrine treatment line for metastatic or inoperable breast cancer exceeding a duration of 1 month;Note:;1. Adjuvant endocrine treatment is not counted as one line.;2. Patients progressing on endocrine treatment: this specific endocrine treatment must have been stopped at least 2 weeks prior to randomization.;- Prior treatment with pertuzumab and/or T-DM1;- Known leptomeningeal or CNS metastases;Note:;A brain MRI or CT scan is mandatory in case of clinical suspicion of CNS metastases.;- Single bone metastasis treated with radiotherapy (if the bone metastasis is the only tumor lesion);- Termination of first-line therapy with trastuzumab/pertuzumab due to unacceptable toxicity without objective evidence of disease progression;- CNS metastases that are untreated, symptomatic, or require therapy to control symptoms, as well as a history of radiation, surgery, or other therapy, including steroids, to control symptoms from CNS metastases within 2 months (60 days) before registration;- Peripheral neuropathy of CTCAE grade *3;- Interstitial lung disease (ILD) or pneumonitis grade *4;- Any other adverse event which has not recovered to CTCAE grade *1 (except alopecia)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	14-01-2015
Enrollment:	26
Type:	Actual

Medical products/devices used

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

Brand name:	T-DM1
Generic name:	Trastuzumab emtansine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-02-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-01-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-08-2018

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-09-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2012-002556-17-NL
ClinicalTrials.gov	NCT01835236
CCMO	NL46227.029.13