Pertuzumab + trastuzumab (PH) versus PH plus metronomic chemotherapy (PHM) in the elderly HER2+ metastatic breast cancer population who may continue on T-DM1 alone following disease progression while on PH / PHM: an open-label multicentre randomized phase II selection trial of the EORTC Elderly Task Force and Breast Cancer Group

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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-OMON41641

Source
ToetsingOnline

Brief title
Elderly met BC: PH vs PHM followed by T-DM1

Condition

- Breast neoplasms malignant and unspecified (incl nipple)

Synonym
mBC, metastatic breast cancer

Research involving
Human

Sponsors and support

Primary sponsor: EORTC
Source(s) of monetary or material Support: EORTC;Pharmacy,Hoffmann-La Roche

Intervention

Keyword: elderly, metastatic breast cancer, pertuzumab, T-DM1, trastuzumab

Outcome measures

Primary outcome

Progression free survival rate at 6 months

Secondary outcome

Overall survival

* Breast cancer specific survival

Safety

* Toxicity (with specific attention to cardiac toxicity);

* Tumor response rate as measured by RECIST v1.1

* For those patients receiving T-DM1 after progression: toxicity, tumor

response, PFS after starting T-DM1

* Evolution of HRQoL as assessed by EORTC QLQ-C30 and ELD 15

* Evolution of geriatric assessment during treatment. This will be based

on the EORTC minimum dataset (G8, IADL and social situation), the

ADL and frailty assessment by SPPB.

-PFS outside of the brain after brain-only relapse for patients continuing on

the treatment they were receiving before brain disease progression (PH or PHM

or T-DM1)

Study description

Background summary

Given the lack of *standard* treatment for older HER-2 positive breast cancer patients and the clear need to have active and tolerable treatment regimens for this population, this will be the first randomized phase II trial to evaluate a chemotherapy-free, anti-HER2-based treatment strategy. This trial will try to answer whether PH combination could delay the use of conventional chemotherapy for very long periods, and in a significant proportion of patients avoid its use altogether. Integration of geriatric evaluation will assist in assessing the benefit of therapy in different ageing populations as well as the impact of the therapy on global functioning.

Study objective

The main objectives are to evaluate the efficacy (as measured by progression free survival at 6 months) of pertuzumab combined with trastuzumab (PH) or PH plus metronomic chemotherapy (PHM) in an elderly metastatic breast cancer population, and to select attractive treatments for further development in Phase III.

Study design

This is an open-label, multicentric, 1:1 randomized phase II selection trial

Intervention

Treatment cycles are defined as a 3 week period.
Arm A: Trastuzumab will be administered at loading dose of 8 mg/kg of body weight on cycle 1, followed by a maintenance dose of 6 mg/kg every 3 weeks. Pertuzumab will be given at a fixed loading dose of 840 mg on cycle 1, followed by 420 mg for subsequent cycles, every 3 weeks.

Arm B: Pertuzumab and trastuzumab will be administered as in arm A. Cyclophosphamide should be taken orally by the patient, at a daily dose of

50 mg/day.

After progression in arm A or arm B, patients will be given the option of receiving T-DM1. T-DM1 will be given at a dose of 3.6 mg/kg IV, every 3 weeks.

Study burden and risks

Risk: possible adverse events from therapy
Benefit: possible active and tolerable treatment

Contacts

Public
EORTC

Av. Emmanuel Mounier 83/11b
Brussel 1200
BE
Scientific
EORTC

Av. Emmanuel Mounier 83/11b
Brussel 1200
BE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

-Female or male patients with histologically proven HER-2 positive (IHC 3+ or or HER-2 gene amplification by in situ hybridization [FISH, SISH].
-Patientsmust have measurable (RECIST v. 1.1) or evaluable disease
-Performance status (PS) 0-3 (WHO)
-Age >= 70 years of age, or >= 60 years old with required number of dependencies as described below :
•65 - 69 in combination with functional restriction defined as limitation in at least 2 of 8 iADL or 1 of 6 ADL or Charlson comorbidity score > 2
•60 - 64 in combination with functional restrictions defined as limitation in at least 3 of 8 iADL 2 of 6 ADL or Charlson comorbidity score > 3
-Life expectancy of more than 12 weeks
-Previous adjuvant chemotherapy/anti HER-2 therapy after surgery is allowed, given that the time interval from end of previous treatment to initiation of treatment for metastatic disease is >=6 months.
-Up to one line of anti-HER therapy (trastuzumab or lapatinib) is allowed in combination with hormone therapy for hormone sensitive metastatic breast cancer.
-Adequate organ function, evidenced by the following laboratory results within 3 weeks prior to randomization: (patients with a buffer range from the normal values of +/- 5% for hematology and +/- 10% for biochemistry [with the EXCEPTION of Glomerular Filtration Rate] are acceptable)
-Absolute neutrophil count > 1500 cells/mm3
-Platelet count > 100,000 cells/mm3
-Hemoglobin > 8.5 g/dL
-Total bilirubin <= 1.5 upper limit of normal (ULN)
-SGOT (AST), SGPT (ALT), and alkaline phosphatase <= 2.5× ULN (for alkaline phosphatase limit applies in the absence of bone metastases)
-Glomerular Filtration Rate (GFR) >= 30 ml/min according to MDRD formula or Cockcroft and Gault Formula
-Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial
-Before patient randomization, written informed consent must be given according to ICH/GCP, and national/local regulations.
-Newly diagnosed or recurrent (after surgery) stage IV disease (TNM/AJCC v.7).

Exclusion criteria

-Current symptomatic brain metastases.
-Prior chemotherapy for metastatic disease.
-Prior treatment with pertuzumab.
-History of exposure to the following cumulative doses of anthracyclines:
•Doxorubicin or liposomal doxorubicin > 360 mg/m2
•Epirubicin > 720 mg/m2
•Mitoxantrone > 120 mg/m2
•Idarubicin > 90 mg/m2
•If another anthracycline or more than 1 anthracycline has been used, then the cumulative dose must not exceed the equivalent of 360 mg/m2 of doxorubicin.
-History of palliative radiotherapy within 14 days of /prior to randomization.
-History of other malignancy within the last 5 years, except for carcinoma in situ of the cervix or basal cell or spinocellular carcinoma of the skin.
-Current uncontrolled hypertension (persistent systolic > 180 mmHg and/or diastolic > 100 mmHg) (with or without medication).
-LVEF below 50%.
-History of significant cardiac disease defined as:
•Symptomatic CHF (NYHA classes II-IV, see Appendix C)
•High-risk uncontrolled arrhythmias, i.e. atrial tachycardia with a heart rate > 100/min at rest, significant ventricular arrhythmia (ventricular tachycardia) or higher-grade AV-block (second degree AV-block Type 2 [Mobitz 2] or third degree AV-block)
•History of myocardial infarction within 6 months prior to randomization
•Clinically significant valvular heart disease
•angina pectoris requiring anti-angina treatment
-Peripheral neuropathy of Grade >=3 per NCI CTCAE version 4.0.
current severe, uncontrolled systemic disease (e.g., clinically significant cardiovascular, pulmonary, or metabolic disease; wound healing disorders; ulcers; or bone fractures, known infection with HIV, active hepatitis B and/or hepatitis C virus)
-Major surgical procedure or significant traumatic injury within 28 days prior to randomization or anticipation of the need for major surgery during the course of study treatment.
-History of receiving any investigational treatment within 28 days of randomization.
-History of intolerance (including Grade 3-4 infusion reaction) to trastuzumab.
-Unwillingness or inability to comply with the requirements of the protocol as assessed by the investigator.

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):	24-04-2014
Enrollment:	7
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Endoxan
Generic name:	Cyclofosfamide
Registration:	Yes - NL intended use
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:	T-DM1
Generic name:	trastuzumab emtansine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	02-10-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	13-03-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-04-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	22-05-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-04-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	27-05-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	17-06-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	24-06-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

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	EUCTR2011-006342-32-NL
CCMO	NL43797.058.13