

Neoadjuvant trastuzumab in patients with HER2-positive locally advanced breast cancer

Submission date 21/04/2009	Recruitment status No longer recruiting	☐ Prospectively registered ☐ Protocol
Registration date 30/04/2009	Overall study status Completed	☐ Statistical analysis plan ☒ Results
Last Edited 15/03/2010	Condition category Cancer	☐ Individual participant data

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
MO16432

Study information

Scientific Title

A multicentre, randomised, controlled, open-labelled trial of paclitaxel-containing chemotherapy (ATT) followed by CMF versus the same chemotherapy plus Herceptin® in women with locally advanced breast cancer and HER2/C-ERBB-2 overexpression and amplification, with a parallel observational study of the same chemotherapy regimen alone, in patients with HER2 negative tumors (0 or 1+ by immunohistochemistry)

Acronym

NOAH

Study objectives

The primary efficacy variable is progression-free survival (PFS). This is defined as the time between randomisation and date of documented relapse or death due to any cause. For patients with HER2-negative disease, randomisation is defined as the date of study registration.

Enrolment of 116 patients was planned for each of the HER2-positive treatment groups in order to provide a total of 86 event-free survival (EFS) events in patients with HER2-positive disease. Assuming 50% EFS rate at 3 years with chemotherapy alone, and a median EFS of 5.5 years with trastuzumab (corresponding to a 68.5% EFS rate at 3 years), a log rank test requires 86 EFS events to achieve 80% power to detect a hazard ratio of 0.545 (absolute improvement of 18.5% in the EFS rate) at a two-sided significance level of 5%.

A sample size of 100 was chosen pragmatically for the parallel group of patients with HER2-negative disease to roughly match the sample size in the two HER2-positive groups, leading to total planned recruitment of 332 patients.

Ethics approval required

Old ethics approval format

Ethics approval(s)

Independent Ethics Committee of the Istituto Nazionale Tumori of Milano (Coordinating Centre) approved on the 23rd April 2002. All other centres will seek ethics approval before recruiting participants.

Primary study design

Interventional

Study design

Multicentre randomised controlled open-labelled trial with a parallel observational study

Study type(s)

Treatment

Health condition(s) or problem(s) studied

Locally advanced breast cancer

Interventions

All patients will receive the same intravenous neoadjuvant chemotherapy regimen: doxorubicin 60 mg/m² plus paclitaxel 150 mg/m² administered over three hours of infusion 3-weekly for three cycles, followed by paclitaxel 175 mg/m² administered 3-weekly for four cycles, followed by cyclophosphamide (600 mg/m²), methotrexate (40 mg/m²) and 5-fluorouracil (600 mg/m²) (CMF) given on day 1 and 8 every 4 weeks for three cycles.

Surgery followed by radiotherapy is scheduled after completion of CMF chemotherapy in all patients. Patients with hormone receptor-positive disease (oestrogen and/or progesterone receptor positive) are planned to receive adjuvant tamoxifen 20 mg/day for 5 years.

Patients randomised to receive trastuzumab will receive a loading dose of 8 mg per kilogram of body weight (mg/kg) infused intravenously over 90 minutes, followed by ten 3-weekly cycles of 6 mg/kg over 30 minutes during chemotherapy. Delivery of trastuzumab every 4 weeks was allowed during CMF chemotherapy. After surgery, seven more cycles of trastuzumab were to be delivered in these patients, starting before or during radiotherapy, to complete a total of one year of trastuzumab treatment (17 or 18 doses).

Total duration of primary systemic treatment is approximately 8 months. The total duration of follow-up is 5 years after surgery

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Intervention Type

Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)

Doxorubicin, paclitaxel, cyclophosphamide, methotrexate, 5-fluorouracil, tamoxifen, trastuzumab

Primary outcome(s)

Event-free survival (EFS), defined as time from randomisation to disease recurrence or progression [local, regional, distant or contralateral] or death due to any cause), measured when 86 EFS events are documented

Key secondary outcome(s)

1. Pathological complete response (in breast pCR [bpCR] and breast and axilla pCR [tpCR]) and overall response rates, measured when all patients complete surgery
2. Cardiac safety in all three groups, measured during primary systemic therapy, before surgery and at two years after surgery
3. Overall survival in all three groups, measured after a median follow-up of 3 and 5 years from registration
4. EFS (measured from study registration) in patients with HER2-negative disease, measured after a median follow-up of 3 years

Completion date

15/12/2005

Eligibility

Key inclusion criteria

1. Female patients, presenting for the first time with locally advanced breast cancer, who have not received any previous treatment for an invasive malignancy
2. Aged greater than or equal to 18 years

3. Eastern Cooperative Oncology Group (ECOG) performance status less than or equal to 1
4. Histologically proven diagnosis of breast cancer
5. Patients may have HER2-negative or -positive disease. HER2-positive disease is defined as follows:
 - 5.1. Overexpresses HER2 by immunohistochemistry (2+ or 3+)
 - 5.2. Has c-erbB2/HER2 amplification according to fluorescent in situ hybridisation (FISH).
 Patients in the parallel observational study must have HER2-negative tumours (0 or 1+) on immunohistochemistry.
6. The primary tumour must be T4 (skin or nipple invasion, peau d'orange, extension into chest wall or inflammatory carcinoma); any T plus N1a, N2 or N3; or any T plus involvement of ipsilateral supraclavicular lymph nodes
7. At least one measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST) criteria (Note: the minimum indicator lesion size is defined as greater than or equal to 20 mm, measured by palpation), except for inflammatory carcinoma (T4d)
8. Have hormonal receptors (oestrogen receptor [ER] and progesterone receptor [PgR]) assessed
9. Signed written informed consent (approved by the Institutional Review Board [IRB] /Independent Ethics Committee [IEC]) obtained prior to any study specific screening procedures
10. Able to comply with the protocol

Participant type(s)

Patient

Healthy volunteers allowed

No

Age group

Adult

Lower age limit

18 Years

Sex

Female

Key exclusion criteria

1. Pregnant or lactating women. Documentation of a negative pregnancy test must be available for pre-menopausal women with intact reproductive organs and for women less than one year after the menopause.
2. Women of childbearing potential unless:
 - 2.1. Surgically sterile
 - 2.2. Using adequate measures of contraception, e.g., intra-uterine device or barrier method of contraception in conjunction with spermicidal jelly
3. Evidence of metastases, with the exception of ipsilateral supraclavicular nodes
4. Bilateral breast cancer
5. Previous treatment with chemotherapy or hormonal therapy or any prior therapy with an anti-HER2 therapy for any malignancy
6. Previous extensive radiotherapy or major surgery for any malignancy
7. Previous or concomitant malignancy of any type, except adequately treated basal cell carcinoma of the skin or in situ cervix cancer
8. Treatment with any investigational drug within 30 days before beginning of treatment with study drugs

9. Patients with New York Heart Association (NYHA) class greater than or equal to II heart disease
10. Patients with a left ventricular ejection fraction (LVEF) less than 50% by multiple gated acquisition (MUGA) scan or echocardiography
11. Other serious illness or medical condition including:
- 11.1. History of documented congestive cardiac failure; angina pectoris requiring antianginal medication; evidence of transmural infarction on electrocardiogram [ECG]; poorly controlled hypertension (e.g. systolic greater than 180 mmHg or diastolic greater than 100 mmHg; however, patients with hypertension which is well controlled on medication are eligible); clinically significant valvular heart disease; or high-risk uncontrolled arrhythmias
- 11.2. Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant precluding informed consent or adversely affecting compliance to study drugs
- 11.3. Serious uncontrolled infections (bacterial or viral) or poorly controlled diabetes mellitus
12. Any of the following abnormal baseline haematological values: neutrophils less than $1.5 \times 10^9/L$, platelets less than $100 \times 10^9/L$
13. Any of the following abnormal laboratory tests: serum total bilirubin greater than $1.25 \times ULN$ (upper limit of normal) (except for patients with clearly documented Gilbert's syndrome), alanine transaminase (ALT) or aspartate transaminase (AST) greater than $1.25 \times ULN$, alkaline phosphatase greater than $1.25 \times ULN$, serum creatinine greater than $1.5 \times ULN$. Hepatic metastases must be excluded as a cause of abnormal liver function tests.

Date of first enrolment

01/06/2002

Date of final enrolment

15/12/2005

Locations

Countries of recruitment

Austria

Germany

Italy

Portugal

Russian Federation

Spain

Study participating centre

Fondazione Istituto Nazionale Tumori

Milano

Italy

20133

Sponsor information

Organisation

Fondazione Michelangelo (Italy)

ROR

<https://ror.org/014vaxq24>

Funder(s)

Funder type

Industry

Funder Name

F. Hoffmann-La Roche Ltd (Switzerland) - provided trastuzumab and financial support

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	30/01/2010		Yes	No