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

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|---|---|---|
| **Submission date**<br>21/04/2009 | **Recruitment status**<br>No longer recruiting | [_] Prospectively registered<br>[_] Protocol<br>[_] Statistical analysis plan<br>[X] Results<br>[_] Individual participant data |
| **Registration date**<br>30/04/2009 | **Overall study status**<br>Completed | |
| **Last Edited**<br>15/03/2010 | **Condition category**<br>Cancer | |

**Plain English summary of protocol**
Not provided at time of registration

## Contact information

**Type(s)**
Scientific

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## Additional identifiers

**EudraCT/CTIS number**

**IRAS number**

**ClinicalTrials.gov number**

**Secondary identifying numbers**
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.

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

## Primary study design
Interventional

## Secondary study design
Randomised controlled trial

## Study setting(s)
Hospital

## Study type(s)
Treatment

## Participant information sheet

## 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/m^2 plus paclitaxel 150 mg/m^2 administered over three hours of infusion 3-weekly for three cycles, followed by paclitaxel 175 mg/m^2 administered 3-weekly for four cycles, followed by cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2) and 5-fluorouracil (600 mg /m^2) (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 measure
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

## Secondary outcome measures
1. Pathlogical 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

### Overall study start date
01/06/2002

### 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

### Age group
Adult

### Lower age limit
18 Years

### Sex
Female

### Target number of participants
Total planned recruitment of 332 patients, 232 in RCT and 100 in observational study

### 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 x 10^9/L, platelets less than 100 x 10^9/L
13. Any of the following abnormal laboratory tests: serum total bilirubin greater than 1.25 x 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 x ULN, alkaline phosphatase greater than 1.25 x ULN, serum creatinine greater than 1.5 x 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
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# Sponsor information

**Organisation**
Fondazione Michelangelo (Italy)

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**Sponsor type**
Research organisation

**Website**
http://www.fondazionemichelangelo.org/

**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

**Publication and dissemination plan**
Not provided at time of registration

**Intention to publish date**

**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 |