ISRCTN96423607 https://doi.org/10.1186/ISRCTN96423607

European Cooperative Study of Primary Systemic Therapy in Women with Operable Breast Cancer and T > 2 cm

Submission date 23/02/2010	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 06/04/2010	**Overall study status** Completed	[_] Statistical analysis plan [_] Results
Last Edited 06/04/2010	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

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
FM-B04-01

Study information

Scientific Title

European Cooperative Study of Primary Systemic Therapy in Women with Operable Breast Cancer and T > 2 cm: a multicentre open-labelled trial with two separate parallel studies

Acronym
ECTO II

Study objectives
The primary efficacy variable of this protocol consisting in two separate and parallel phase II studies is the rate of pathological complete remissions (pCR = absence of invasive cancer cells at pathological examination) assessed at surgery after primary systemic therapy in ER-negative (Study 1) and in ER-positive (Study 2) early breast cancer.

In ER-negative tumours, prior experience revealed that after 4 cycles of AT (doxorubicin [Adriamycin®] and paclitaxel [Taxol®]) followed by 4 cycles of CMF (Cyclophosphamide, Methotrexate, Flourouracil), the rate of pCR was 46%. Patients eligible for Study 1 will be randomly allocated to one of three arms and for each study regimen an absolute increase of the pCR rate of at least 15% . An important secondary endpoint of the study is to decide which of the three regimens is the most promising. This will be addressed based on a randomised phase II trial design proposed by Simon et al. in 1985 and updated in 2002. For ER-negative tumours a pCR rate > 50% is considered to be of clinical interest. Therefore, the null hypothesis is set at 50% vs an alternative hypothesis of a pCR rate of 65%. In order to have a 90% probability of selecting a treatment regimen if it has at least a 15% better activity than the others, 105 patients are to be randomly assigned to each of the three regimens. This would assume that the response rate in the less efficacious arm(s) is 50%. No formal comparison between the three arms is planned. Instead, the regimen(s) with the best response rate will be declared the winner (s) provided its (their) response rate is greater that 50%. From the above, a total of 315 patients with ER-negative tumours would be needed. At the first stage of accrual, a total of 42 patients are needed for each of the three regomens and accrual to the study will be continued for those of the arms where at least 23 pCR have been documented.

In ER-positive tumours, prior experience revealed that after 4 cycles of AT followed by 4 cycles of CMF, the rate of pCR was 11%. Patients eligible for Study 2 will be randomly allocated to one of three arms and for each study regimen an absolute increase of the pCR rate of at least 15%. An important secondary endpoint of the study is to decide which of the three regimens is the most promising. This will be addressed based on a randomized phase II trial design proposed by Simon et al. in 1985 and updated in 2002. For ER-positive tumours a pCR rate > 10% is considered to be of clinical interest. Therefore, the null hypothesis is set at 10% vs an alternative hypothesis of a pCR rate of 25%. In order to have a 90% probability of selecting a treatment regimen if it has at least a 15% better activity than the others, 57 patients are to be randomly assigned to each of the three regimens. This would assume that the response rate in the less efficacious arm(s) is 10%. No formal comparison between the three arms is planned. Instead, the regimen(s) with the best response rate will be declared the winner(s) provided its (their) response rate is greater that 10%. From the above, a total of 171 patients with ER-positive tumours would be needed. At the first stage of accrual, a total of 28 patients are needed for each of the three regimens and accrual to the study will be continued for those of the arms where at least 4 pCR have been documented.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Independent Ethics Committee of the Istituto Nazionale Tumori of Milano (Coordinating Center) approved on the 24th February 2005 (ref: INT 21/05)
All other centres will seek ethics approval before recruiting participants.

Study design
Multicentre open-labelled trial with two separate parallel studies

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Early invasive unilateral breast cancer larger than 2 cm in diameter

Interventions
1. Patients in Study 1 will randomly receive one of the three following regimens
1.1. AT: doxorubicin (60 mg/ m^2) plus paclitaxel (200 mg/m^2) every 3 weeks for 4 cycles sequentially followed by CMF: cyclophosphamide (600 mg/m2^), methotrexate (40 mg/m^2) and fluorouracil (600 mg /m^2) by intravenous administration on day 1 and 8, every 4 weeks for 4 cycles.
1.2. AT: doxorubicin (60 mg/ m^2) plus paclitaxel (200 mg/m^2) every 3 weeks for 4 cycles sequentially followed by CM: cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2) by intravenous administration on day 1 and 8 every 4 weeks for 4 cycles plus Capecitabine (Xeloda® [X]) to be administered orally from day 1 to day 14 of each cycle at the dose of 1850 mg/m^2 (to be divided in two daily doses, within half an hour from breakfast and dinner, with a glass of water) for 4 cycles.
1.3. AC: doxorubicin (60 mg/ m^2) plus cyclophosphamide (600 mg/m^2) every 3 weeks for 4 cycles sequentially followed by Paclitaxel (100 mg/m^2) on day 1 and 8 every 3 weeks for 4 cycles plus Capecitabine (Xeloda® [X]) to be administered orally from day 1 to day 14 of each cycle at the dose of 1850 mg/m^2 (to be divided in two daily doses, within half an hour from breakfast and dinner, with a glass of water) for 4 cycles.

Patients in Study 2 will randomly receive one of the three following regimens
1) AT: doxorubicin (60 mg/ m^2) plus paclitaxel (200 mg/m^2) every 3 weeks for 4 cycles sequentially followed by CMF: cyclophosphamide (600 mg/m2^), methotrexate (40 mg/m^2) and fluorouracil (600 mg /m^2) by intravenous administration on day 1 and 8 every 4 weeks for 4 cycles. Exemestane will be administered daily at the oral dose of 25 mg from the first day of doxorubicin and paclitaxel till the day of surgery. Luteinizing Hormone-Releasing Hormone (LH-RH) analogues must be delivered in premenopausal patients to achieve total estrogen blockade.
2) AT: doxorubicin (60 mg/ m^2) plus paclitaxel (200 mg/m^2) every 3 weeks for 4 cycles sequentially followed by CM: cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2) by intravenous administration on day 1 and 8 every 4 weeks for 4 cycles plus Capecitabine (Xeloda® [X]) to be administered orally from day 1 to day 14 of each cycle at the dose of 1850 mg/m^2 (to be divided in two daily doses, within half an hour from breakfast and dinner, with a glass of water) for 4 cycles. Exemestane will be administered daily at the oral dose of 25 mg from the first day of doxorubicin and paclitaxel till the day of surgery. LH-RH analogues must be delivered in premenopausal patients to achieve total estrogen blockade.
3) AC: doxorubicin (60 mg/ m^2) plus cyclophosphamide (600 mg/m^2) every 3 weeks for 4

cycles sequentially followed by paclitaxel (100 mg/m^2) on day 1 and 8 every 3 weeks for 4 cycles plus capecitabine (Xeloda® [X]) to be administered orally from day 1 to day 14 of each cycle at the dose of 1850 mg/m^2 (to be divided in two daily doses, within half an hour from breakfast and dinner, with a glass of water) for 4 cycles. Exemestane will be administered daily at the oral dose of 25 mg from the first day of doxorubicin and cyclophosphamide till the day of surgery. LH-RH analogues must be delivered in premenopausal patients to achieve total estrogen blockade.

Surgery (followed by radiotherapy if breast conserving) is scheduled after completion of the systemic therapy in all patients.

Although disease-free and overall survival are not the main objectives of this study, we recommended that all patients be followed for at least the first 5 years after the end of the planned treatment to comply with Good Clinical Practice (GCP) rules on long-term safety of study drugs.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
AT: Doxorubicin (Adriamycin®), paclitaxel (Taxol®); CMF: cyclophosphamide, methotrexate, flourouracil; X: capecitabine (Xeloda®); exemestane (Aromasin®)

Primary outcome(s)
Pathological complete response in breast (pCR), defined as the absence of invasive cancer cells at pathological examination, measured when all patients complete surgery

Key secondary outcome(s))
1. Overall response rate measured when patients complete primary systemic therapy
2. Tolerability and safety of all proposed regimens

Completion date
18/12/2008

Eligibility

Key inclusion criteria
1. Female patients, presenting for the first time with unilateral operable breast cancer larger than 2.0 cm in largest diameter, who have not received any previous treatment for an invasive malignancy
2. Histologically proven diagnosis of invasive breast cancer
3. Estrogen receptor status assessed as negative (Study 1) or positive (Study 2)
4. Age greater than or equal to 18 years
5. Eastern Cooperative Oncology Group (ECOG) Performance Status less than or equal to 1
6. Availability of Human EGF (Epidermal Growth Factor) Receptor 2 (HER2) status on immunohistochemistry
7. Availability of progesterone receptor status
8. Primary tumour lesion measurable on largest diameter by clinical and/or radiological

examination. Presence of suspected multifocal disease does not exclude the patient
9. Patients must have completed all instrumental and laboratory evaluations within 4 weeks prior to study entry
10. Signed written informed consent (approved by the Institutional Review Board [IRB]/ Independent Ethics Committee [IEC]) obtained prior to any study specific screening procedures
11. 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 premenopausal women with intact reproductive organs and for women less than one year after the menopause
2. Women of childbearing potential unless (1) surgically sterile or (2) using adequate measures of contraception. For example: intra-uterine device or barrier method of contraception in conjunction with spermicidal jelly
3. Evidence of metastases or locally advanced breast cancer
4. Bilateral breast cancer
5. Absence of ER assessment
6. Previous treatment with chemotherapy or hormonal therapy or any prior therapy with any investigational drug for any type of malignancy
7. Previous extensive radiotherapy or major surgery for any malignancy
8. Previous or concomitant malignancy of any type, except adequately treated basal cell carcinoma of the skin or in situ cervix cancer
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) below 50% by Multiple Uptake Gated Acquisition (MUGA) scan or echocardiography
11. Pre-existing motor or sensory neuropathy of grade greater than 1 for any reason
12. Patients with a history of hypersensitivity due to administration of drugs containing polyoxyethylene castor oil (Cremophor EL) (e.g., cyclosporin), or hardened castor oil (e.g., vitamin preparations for injection, etc.)
13. Other serious illness or medical condition including:
13.1. History of documented congestive cardiac failure
13.2. Angina pectoris requiring antianginal medication
13.3. Evidence of transmural infarction on ECG
13.4. Poorly controlled hypertension (e.g. systolic greater than 180 mm Hg or diastolic greater than 100 mm Hg; however, patients with hypertension which is well controlled on medication

are eligible)
13.5. Clinically significant valvular heart disease
13.6. High-risk uncontrolled arrhythmias
14. Patients with a history of uncontrolled seizures, central nervous system disorders or psychiatric disability judged by the investigator to be clinically significant and precluding informed consent or adversely affecting compliance to study drugs
15. Serious uncontrolled infections (bacterial or viral) or poorly controlled diabetes mellitus
16. Any of the following abnormal baseline haematological values:
16.1. Neutrophils less than 1.5 x10^9/L
16.2. Platelets less than 100 x 10^9/L
17. Any of the following abnormal laboratory tests:
17.1. Serum total bilirubin greater than 1.25 xULN (upper limit of normal) (except for patients with clearly documented Gilberts syndrome)
17.2. Alanine transaminase (ALT) or aspartate transaminase (AST) greater than 1.25 x ULN
17.3. Alkaline phosphatase greater than 1.25 x ULN
17.4. Serum creatinine greater than 1.5 x ULN

Date of first enrolment
30/06/2005

Date of final enrolment
18/12/2008

Locations

Countries of recruitment
Austria

Germany

Italy

Russian Federation

Spain

Study participating centre
Fondazione IRCCS Istituto Nazionale Tumori
Milano
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Sponsor information

Organisation
Fondazione Michelangelo (Italy)

ROR
https://ror.org/014vaxq24

Funder(s)

Funder type
Charity

Funder Name
Michelangelo Foundation (Fondazione Michelangelo) (Italy)

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?
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes