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Pre-surgical effects of serms, anti-COX-2 and aromatase inhibitors in breast cancer patients

Submission date
21/08/2012

Recruitment status
No longer recruiting

Registration date
11/09/2012

Overall study status
Completed

Last Edited
11/04/2019

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
The development of breast cancer is a complex process that results in different types of tumors requiring different treatments. Drug treatment before surgery can have a clinical benefit by reducing tumour growth. The aim of this study is to assess the effectiveness of four drugs in patients awaiting surgery for breast cancer: tamoxifen and raloxifene in premenopausal women, and exemestane and celecoxib in postmenopausal women.

Who can participate?
Women aged 18 or over with breast cancer who are awaiting surgery

What does the study involved?
A biopsy (sample) of the cancer and a blood sample are taken from all participants. Premenopausal women are randomly allocated to be treated with either low-dose tamoxifen or raloxifene or placebo (dummy drug), while postmenopausal women are randomly allocated to be treated with either exemestane or celecoxib or placebo. Tumor growth is assessed at the start of the study and after 6 weeks of drug treatment.

What are the possible benefits and risks of participating?
This study will provide important information for the development of breast cancer treatment. For the short period of treatment no serious adverse effects are expected. For the same reason a clinical benefit is not expected, although a small shrinkage of the tumor might be possible. The main aim is to slow down tumor growth.

Where is the study run from?
European Institute of Oncology (Italy)

When is the study starting and how long is it expected to run for?
February 2004 to March 2009

Who is funding the study?
European Institute of Oncology (Italy)

Who is the main contact?
Dr Bernardo Bonanni

Contact information

Type(s)
Scientific

Contact name
Dr Bernardo Bonanni

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Additional identifiers

Protocol serial number
IEO S162/303

Study information

Scientific Title
Pre-surgical effects of serms, anti-COX-2 and aromatase inhibitors in breast cancer patients: a phase II randomized controlled trial

Study objectives
The primary objective of the trial is to assess antiproliferative activity of the different drugs compared with placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
European Institute of Oncology Ethics Committee [Comitato Etico dell'Istituto Europeo di Oncologia], 02/10/2003, ref: CC/13/04

Study design
Presurgical randomized phase II single-centre trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Estrogen receptor positive breast cancer

Interventions
Breast cancer patients are randomized based on menopausal status to Raloxifene or Tamoxifen or placebo, to Exemestane or Celecoxib or placebo.

Subjects with histologically-confirmed ER positive primary breast cancer will be randomly assigned in a 2:2:1 ratio to receive treatment or matching placebo for a total period of 6 weeks prior to surgery. Specifically, 125 premenopausal women will be randomized to either low-dose tamoxifen (10 mg/week) or raloxifene 60 mg/day or placebo, while 125 postmenopausal women will be allocated to exemestane (25 mg/day) or celecoxib (800 mg/day) or placebo.

Raloxifene: Evista® 60 mg/tablet. Daily administration.
Tamoxifen: Nomafen® 10 mg/tablet. Weekly administration.
Exemestane (Aromasin®): 25 mg/tablet. Daily administration.
Celecoxib: (Celebrex®) 200 mg/tablet. Two tablets will be administered twice a day

Placebo formulation of size-matched tablets will be manufactured by an external pharmaceutical service.

At randomization each subject will receive 1 box with 8 weekly bottles of the drug and will be instructed to take 1 tablet per day. However, in order to maintain the blinding of a weekly dose of tamoxifen in the premenopausal group, each subject will receive also 8 blisters with 1 tablet each. She will be asked to take 2 tablets the first day of the week, 1 from the bottle and 1 from the blister, and then proceed with 1 tablet/day for the rest of the week. Blisters will contain placebo or tamoxifen accordingly.
A regards the post menopausal group, given the unnecessary use of 3 extra placebo tablets, double-blinding will be maintained for exemestane and placebo (1 tablet/day) only, while the celecoxib arm will be open (2 tablets twice a day).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Tamoxifen, raloxifene, exemestane, celecoxib

Primary outcome(s)
The primary endpoint is the change (tru-cut biopsy at baseline, and surgical specimen at surgery) in the percentage of neoplastic cells expressing the proliferation antigen Ki-67.

Biopsy and surgical specimens are fixed in 10% neutral-buffered formalin for 6-8 hours before being embedded in paraffin. Sections (4-micron thick) are cut and stained with hematoxylin and eosin. Consecutive serial sections are used for immunohistochemical determinations. Expression Ki-67 will be determined by immunohistochemistry. Briefly, de-waxed tumor sections are pretreated with 3% hydrogen peroxide for 5 minutes to block endogenous peroxidase activity

and then treated with a solution of 0.001 M EDTA (pH 8.0) at 99°C for 20 minutes to retrieve antigens. The tumor sections are then incubated with primary mouse monoclonal antibodies Ki-67 (clone Mib-1, 1:200 dilution).

Primary endpoints will be detected at baseline and after 6 weeks of treatment (at biopsy and at surgery)

Key secondary outcome(s))
Secondary endpoints: Change in ER and PgR expression and apoptosis as measured by Caspase-3. Change in markers of hemostasis and inflammation: fibrinogen, antithrombin III (AT III), plasminogen activator inhibitor-I (PAI-I), ultrasensitive C-reactive protein (US-CRP). Change in circulating hormones (estradiol, estrone, estrone-sulphate, and sex hormone binding globulin). DNA will be extracted from circulating lymphocytes and some genetic polymorphisms related to hormone and drug metabolism will be investigated.

Expression of ER, PgR, Her2/neu, and Caspase-3 will be determined by immunohistochemistry. The tumor sections are then incubated with primary mouse monoclonal antibodies to ER (clone 1D5, 1:100 dilution), PgR (clone 1A6, 1:800 dilution), or with rabbit polyclonal antibody to the Her2/neu protein (1:3200 dilution), and to Caspase-3 (clone CPP32).
Routine hematology and biochemistry assessments will be performed at the central laboratory of the institute.
IGF-I levels will be determined from plasma by a chemiluminescent immunometric assay; antithrombin-III will determined by a kinetic colorimetric method. Serum concentration of US-CRP, SHBG and IGFBP-3 will be measured by a two-site chemiluminescent enzyme immunometric assay. Serum C-telopeptide and osteocalcin will be determined with a electrochemiluminescent immunometric assay. Serum estradiol and estrone-sulphate will be determined by the use of commercially available ultrasensitive radioimmunoassay kits.
Genomic DNA will be extracted from frozen whole blood samples stabilized with EDTA by the use of a commercially available kit (QIAamp DNA Blood kit) purchased from Qiagen S.p.A, Milan, Italy).The evaluation of the CYP2D6 single nucleotide polymorphisms will be performed utilizing a semiautomated instrument (Light Cycler Roche) that allows more rapid assay procedures and guarantees a good product specificity. Specific primers and probes are labeled with fluorescent dyes and light emission monitored to detect genotyping.

Secondary endpoints will be detected at baseline and after 6 weeks of treatment (at biopsy and at surgery)

Completion date
31/03/2009

Eligibility

Key inclusion criteria
1. Female, aged at least 18 years old, no upper age limit
2. Performance status = 0 (SWOG)
3. Histologically-confirmed ER+ primary breast cancer candidated for conservative surgery
4. Stage T1-2, N0-1, M0 or women with larger tumors who refuse chemo and/or endocrine therapy before surgery
5. No previous treatment for breast cancer
6. Provision of written informed consent

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Total final enrolment
125

Key exclusion criteria
1. Previous treatment for breast cancer including chemotherapy and endocrine therapy
2. Patients eligible to neoadjuvant chemo and/or endocrine therapy
3. Evidence of previous superficial or deep venous thrombosis or other thrombo-embolic events of relevance (pulmonary embolism, stroke, etc)
4. Current anti-coagulant therapy
5. Moderate to severe alteration in hematologic profile, hemostasis, renal and hepatic metabolism
6. Clinically active peptic ulcer or gastroenteric disease
7. Severe retinal disease
8. Severe endometriosis (grade III-IV) or other proliferative disorders of the endometrium
9. Clinically active neurologic or psychiatric disease
10. Other medical contraindications as judged by the investigator
11. Other co-existing malignancies or malignancies diagnosed within the last 5 years with the exception of basal cell carcinoma or cervical cancer in situ
12. Pregnancy or current breast feeding (women of child-bearing potential must have a negative pregnancy test within 7 days before the start of study treatment)

Date of first enrolment
17/02/2004

Date of final enrolment
31/03/2009

Locations

Countries of recruitment
Italy

Study participating centre

European Institute of Oncology
Milano
Italy
20141

Sponsor information

Organisation
European Institute of Oncology [Fondazione Istituto Europeo di Oncologia (FIEO)] (Italy)

ROR
https://ror.org/02vr0ne26

Funder(s)

Funder type
Research organisation

Funder Name
European Institute of Oncology Foundation [FIEO] (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?
Results article	results	01/02/2020	11/04/2019	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes