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MINDACT (Microarray In Node-negative Disease may Avoid Chemotherapy): a prospective, randomised study comparing the 70-gene signature with the common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in node-negative breast cancer

Submission date
18/12/2007

Recruitment status
No longer recruiting

Registration date
20/03/2008

Overall study status
Completed

Last Edited
24/03/2022

Condition category
Cancer

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

Plain English summary of protocol
http://www.cancerhelp.org.uk/trials/a-trial-comparing-different-ways-of-deciding-on-treatment-after-surgery-different-types-of-chemotherapy-and-different-types-of-hormone-therapy-for-breast-cancer

Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT00433589

Protocol serial number
EORTC 10041 BIG 3-04

Study information

Scientific Title
MINDACT (Microarray In Node-negative Disease may Avoid Chemotherapy): a prospective, randomised study comparing the 70-gene signature with the common clinical-pathological criteria in selecting patients for adjuvant chemotherapy in node-negative breast cancer

Acronym
MINDACT

Study objectives
The primary purpose is to see whether the gene array signature (genomic prognosis) is superior to conventional clinical pathology parameters (clinical prognosis) in determining which patients would benefit from chemotherapy. Ultimately this should determine which patients who currently receive chemotherapy do not benefit from the chemotherapy and the value of conventional and gene array signature in separating out these women. In future this could save women who might not benefit from receiving chemotherapy. In addition two different chemotherapy regimens and two different hormonal therapy regimens will be compared.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from the Brighton East Research Ethics Committee on 01/08/2007 (ref: 07/Q1907/52)

Study design
Phase III randomised superiority trial with three randomisations

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Breast cancer

Interventions
MINDACT is a phase III randomised superiority trial with three randomisations to compare clinical-pathological risk assessment using the 70-gene signature. It will also assess the efficacy of commonly used anthracycline-based chemotherapy regimens, selected from a list of acceptable regimens, to the new capecitabine-docetaxol combination. In addition the long term safety and efficacy of two years tamoxifen followed by five years of letrozole will be investigated. Node-negative women, will be offered those randomisations for which they are eligible. Eligibility will be determined depending on an individual's clinical and genomic risk assessments, the consequent decision to administer chemotherapy, and their eligibility for

endocrine therapy. In addition, all ER positive patients are offered randomisation to: seven years letrozole or two years tamoxifen then five years letrozole in a ratio of 1:1.

Patients randomised to chemotherapy are randomised to one of two treatment arms:

Arm 1 anthracycline-based:
Patients may receive one of the following regimens:
1. FEC 100: fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2, all intravenous (iv) every three weeks for six cycles
2. Canadian CEF: cyclophosphamide orally 75 mg/m^2 on days 1 - 14, epirubicin 60 mg/m^2 iv on days 1 and 8, fluorouracil 500 mg/m^2 iv on days 1 and 8, every four weeks for six cycles. If oral cyclophosphamide is not tolerated, it may be switched to iv doses of 370 mg/m^2 on days 1 and 8
3. FAC: cyclophosphamide 500 mg/m^2 on day 1, doxorubicin 50 mg/m^2 iv on day 1, fluorouracil 500 mg/m^2 iv on day 1, every three weeks for six cycles
4. CAF: cyclophosphamide 600 mg/m^2 on day 1, doxorubicin 60 mg/m^2 iv on day 1, fluorouracil 600 mg/m^2 iv on days 1 and 8, every four weeks for six cycles
5. E-CMF: epirubicin 100 mg/m^2 on day 1 every three weeks for four cycles followed by either classical CMF (cyclophosphamide orally 100 mg/m^2 on days 1 - 14, methotrexate 40 mg/m^2 iv on days 1 and 8 and 5-fluorouracil 600 mg/m^2 iv on days 1 and 8) every four weeks for four cycles or iv dose modified CMF (750 mg/m^2, 50 mg/m^2 and 600 mg/m^2 respectively on day 1) every three weeks for four cycles

Each treatment will be given as scheduled (three or four weeks) ± 3 days. 5-fluorouracil may be administered as an iv bolus over 15 minutes or less, epirubicin as an iv infusion over 1 hour, doxorubicin as an iv bolus in 10 to 15 minutes, cyclophosphamide as an iv infusion over 1 hour or less and methotrexate as an iv bolus.

Arm 2 docetaxol and capecitabine:
Patients receive docetaxol (75 mg/m^2) iv over 1 hour on day 1 and oral capecitabine (825 mg /m^2) twice daily on days 1 - 14. Treatment repeats every three weeks for six courses.

Patients randomised to endocrine therapy are randomised to:
1. Two years of tamoxifen followed by five years of letrozole, or
2. Seven years of letrozole

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Anthracycline, fluorouracil, epirubicin, cyclophosphamide, doxorubicin, methotrexate, docetaxol, capecitabine, tamoxifen, letrozole

Primary outcome(s)
Survival based on molecular profiling compared with clinical pathology assessment:
1. Distant metastasis free survival is calculated as the time from enrolment/randomisation to

either the first date of distant metastatic recurrence or the date of death
2. Disease free survival is calculated as the time from enrolment/randomisation to either the date of disease progression or the date of death

Key secondary outcome(s))
Estimates of efficacy for each treatment strategy.

Completion date
01/01/2017

Eligibility

Key inclusion criteria
To be eligible for the MINDACT trial patients will have to comply with the following eligibility criteria, which demonstrate that the patients have early non-metastatic breast cancer:
1. Women with histologically proven operable invasive breast cancer and a negative sentinel node or negative axillary clearance (N0, M0). Acceptable primary treatment options are:
1.1. Breast conserving surgery or mastectomy with either a sentinel node procedure or full axillary clearance
1.2. Radiotherapy is mandatory in the case of breast conserving surgery and will be administered according to local institutional policy after mastectomy
1.3. Patients with unresectable positive deep margins who receive adjuvant radiotherapy are eligible provided that all other margins are negative
2. A tumour clinical classification of T1, T2 or operable T3
3. The breast tumour must be unilateral, however ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS) are allowed if invasive cancer is present
4. A frozen tumour sample (not fixed in formalin) must be available for inclusion. The tumour sample must be taken from the excised primary tumour (a core punch biopsy).
5. Patients should: be aged between 18 and 70 years at randomisation (elderly patients for whom adjuvant treatment is considered could be offered participation in one of the BIG Elderly trials)
6. Have a World Health Organization (WHO) performance status of 0 or 1
7. Have adequate bone marrow reserves (neutrophil count greater than 1.5 x 10^9/l and platelet count greater than 100 x 10^9), adequate renal function (creatinine clearance greater than or equal to 50 mL/min [calculated according to Cockroft and Gault], or serum creatinine less than or equal to 1.5 x upper limit of normal), hepatic function (alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT] less than or equal to 2.5 x upper limit of normal, alkaline phosphatase less than or equal to 2.5 x upper limit of normal, total bilirubin less than or equal to 2.0 x upper limit of normal) and normal electrocardiogram (ECG) compatible with chemotherapy administration
8. While taking study medications patients should take adequate birth control measures which result in low failure rates (i.e. less then 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some intra-uterine devices (IUDs), sexual abstinence or vasectomised partner (Note 3 of the guidance on non-clinical safety studies for the conduct of human clinical trials for pharmaceuticals CPMP/ICH/286/95)
9. Signed written informed consent must be given according to International Conference on Harmonisation Good Clinical Practice (ICH GCP), and national/local regulatory requirements before enrolment in the trial (both a screening patient information sheet [PIS] and informed consent [IC] and the PIS and IC 1 must be signed before enrolment)

Patients will be eligible for inclusion in the chemotherapy randomisation (R-C) if they meet all of the general eligibility criteria AND the following criteria:
10. Women who have:
10.1. A high risk of recurrence according to both the clinical-pathological criteria and the 70-gene signature, or
10.2. A high risk according to the clinical-pathological criteria and a low-risk according to the 70-gene signature, and were randomised (R-T) to use the clinical-pathological criteria for chemotherapy decision, or
10.3. A low-risk according to the clinical-pathological criteria and a high-risk according to the 70-gene signature and were randomised (R-T) to use the 70-gene signature for chemotherapy decision
11. WHO status 0 or 1
12. Have cardiac function (left ventricular ejection fraction [LVEF] within the normal limits of each institution, measured either by echocardiography or by radionuclide angiocardiography [multiple gated acquisition scan - MUGA]) according to the standard of care
13. Written informed consent (PIS and IC 2) prior to beginning specific protocol chemotherapy procedures, to be given and documented according to ICH GCP and national/local regulatory requirements
14. Interval between definitive surgery and start of chemotherapy should ideally be no more than six weeks but cannot exceed eight weeks
15. NOT have had any organ allografts requiring immunosuppressive therapy
16. NOT have a requirement for concurrent use of the antiviral agent sorivudine (antiviral) or chemically related analogues, such as brivudine
17. NOT have a history of severe hypersensitivity reaction to drugs formulated with polysorbate 80
18. Have physical integrity of the upper gastrointestinal tract, ability to swallow tablets, and NO malabsorption syndrome

Patients who meet all the general eligibility criteria and who have endocrine responsive disease AND meet the following criteria will be offered the endocrine therapy randomisation (R-E):
19. Are hormone receptor positive, either oestrogen (ER), progesterone (PgR) or both
20. Have given written informed consent (PIS and IC 3) prior to beginning specific protocol endocrine therapy procedures, according to ICH GCP and national/local regulatory requirements
21. NOT have a prior history of thromboembolic disorder, deep vein thrombosis (DVT) or pulmonary emboli
22. Premenopausal women must have ovarian function suppression during endocrine therapy with aromatase inhibitor
23. Patients must not have previously received high dose systemic corticosteroids (except as part of their anti-emetic treatment), immunotherapy or biological response modifiers (e.g., interferon)
24. Hormone replacement therapy (HRT) must be stopped at least four weeks before trial endocrine treatment is initiated
25. Patients who have received adjuvant anti-oestrogen therapy for more than one month immediately following surgery, radiotherapy, and/or chemotherapy may NOT be proposed enrolment in the endocrine question of the trial
26. Women with a history of breast cancer chemoprevention with anti-oestrogens can be included if at least 18 months has elapsed between discontinuation of chemoprevention and clinical or radiological diagnosis of breast cancer

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Female

Key exclusion criteria
1. Serious cardiac illness or medical condition including but not confined to:
1.1. A history of documented congestive heart failure (CHF)
1.2. High-risk uncontrolled arrhythmias
1.3. Angina pectoris requiring antianginal medication
1.4. Clinically significant valvular heart disease
1.5. Evidence of transmural infarction on ECG
1.6. Poorly controlled hypertension (e.g. systolic blood pressure [BP] greater than 180 mmHg or diastolic BP greater than 100 mmHg)
1.7. Symptomatic coronary artery disease
1.8. A myocardial infarction
Within the last 12 months or other risk factors that contra-indicate the use of anthracycline-based chemotherapy
2. Previous or concurrent cancer, possible exceptions are:
2.1. Adequately treated carcinoma in situ of the cervix
2.2. Non-melanoma skin cancer
2.3. Any cancer (other than breast cancer) in complete remission for greater than or equal to five years
3. Serious uncontrolled intercurrent infections, or other serious uncontrolled concomitant disease
4. Received previous chemotherapy, hormonal therapy or radiotherapy
5. Participated in any investigational drug study within the four weeks preceding the start of treatment
6. Be pregnant or breast-feeding at the time of diagnosis or randomisation. A woman of childbearing potential must have a negative pregnancy test. If post-menopausal, the woman must have been amenorrhoeic for at least 12 months to be considered of non-childbearing potential.
7. Any psychological, familial, sociological, geographical or serious uncontrolled medical (e.g. a history of uncontrolled seizures, central nervous system disorders, or psychiatric disability) condition judged by the investigator to be clinically significant which could potentially preclude informed consent or interfere with compliance for oral drug intake or with the study protocol and follow-up schedule. These conditions should be discussed with the patient before enrolment in the trial.

Date of first enrolment
07/03/2007

Date of final enrolment
01/01/2017

Locations

Countries of recruitment
United Kingdom

Scotland

Belgium

France

Netherlands

Slovenia

Spain

Study participating centre
Department of Surgery & Molecular Oncology
Dundee
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Sponsor information

Organisation
European Organisation for Research and Treatment of Cancer (EORTC) (Belgium)

ROR
https://ror.org/034wxcc35

Funder(s)

Funder type
Charity

Funder Name
Cancer Research UK (CRUK) (UK) (ref C7636/A7714) - Clinical and Translational Research Directorate

Results and Publications

Individual participant data (IPD) sharing plan
Not provided at time of registration

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	18/06/2013		Yes	No
Plain English results			24/03/2022	No	Yes