ISRCTN15094808 https://doi.org/10.1186/ISRCTN15094808

Response to optimal selection of neo-adjuvant chemotherapy in operable breast cancer

Submission date 03/06/2015	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol [_] Statistical analysis plan [_] Results [_] Individual participant data [X] Record updated in last year
Registration date 03/06/2015	**Overall study status** Ongoing	
Last Edited 02/07/2025	**Condition category** Cancer	

Plain English summary of protocol
http://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-trial-looking-at-2-new-tests-to-help-select-chemotherapy-before-surgery-for-breast-cancer-rosco

Study website
https://www.birmingham.ac.uk/research/crctu/trials/rosco/index.aspx

Contact information

Type(s)
Public

Contact name
Dr Sarah Bowden

Contact details
Cancer Research UK
Institute for Cancer Studies
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT
0121 414 8040
S.J.Bowden@BHam.ac.uk

Additional identifiers

EudraCT/CTIS number
2013-004307-39

IRAS number

129176

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
19069

Study information

Scientific Title
Response to Optimal Selection of neo-adjuvant Chemotherapy in Operable breast cancer: a randomised phase III, stratified biomarker trial of neo--adjuvant 5-Fluorouracil, Epirubicin and Cyclophosphamide vs Docetaxel and Cyclophosphamide chemotherapy

Acronym
ROSCO

Study objectives
Neoadjuvant chemotherapy (NAC), for early breast cancer reduces the amount of surgical treatment required, often avoiding the need for mastectomy. A pathological complete response (pCR) is generally associated with excellent prognosis and no pCR is associated with poor outcomes. To maximise pCR, patients are treated with both epirubicin and docetaxel containing combinations increasing toxicity due to exposure to both drugs. Retrospective analysis of adjuvant chemotherapy trials strongly suggests that a combination of two genetic markers (CEP17 and TOP2A) predict for epirubicin sensitivity. It may be unnecessary to treat all patients with both epirubicin and docetaxel. Current standard of care in patients with involved axillary nodes before chemotherapy is an axillary dissection. When there is no residual cancer this becomes an unnecessary procedure. The data on the use of sentinel lymph node biopsy post NAC is controversial. In ROSCO, 1056 patients with early breast cancer will be randomised from hospitals around the UK to initial chemotherapy with either epirubicin based or docetaxel based chemotherapy. They will be stratification by CEP17 and TOP2A status. On completion of 4 cycles of chemotherapy patients will undergo surgery and pCR assessment. Where pCR is not achieved, patients will receive the alternative chemotherapy as adjuvant treatment. The aim is to determine if CEP17 and TOP2A status can be used to select the appropriate chemotherapy, resulting in higher pCR rates and a requirement for less chemotherapy. Patients with axillary node involvement prechemotherapy will undergo a post NAC, sentinel node biopsy (SLNB) and axillary clearance as a single procedure to determine if post NAC SLNB is sufficiently accurate to be used as a routine staging tool in this context.

Ethics approval required
Old ethics approval format

Ethics approval(s)
First MREC approval date 08/12/2014, ref: 14/WM/1213

Study design
Randomized; Interventional; Design type: Treatment

Primary study design

Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details to request a patient information sheet

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

Interventions
1. Surgery (combined SLNB and axillary node clearance will be mandatory in all patients with clinically or pathologically involved nodes prior to chemotherapy)
2. All HER2 positive patients will receive Trastuzumab at 8 mg/kg with first cycle of chemotherapy followed by 6 mg/kg 3 weekly for 6-12 months; TC - surgery - FEC, Docetaxel 75 mg/m2, cyclophosphamide 600 mg/m2

Follow Up Length: 120 month(s)
Study Entry : Registration and One or More Randomisations

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Cyclophosphamide, docetaxel, epirubicin, 5-fluorouracil, Herceptin (trastuzumab)

Primary outcome measure
Complete pathological response (pCR) rate; Timepoint(s): On completion of 4 cycles of NAC

Secondary outcome measures
1. Clinical response in breast alone; Timepoint(s): After 4 cycles of NAC
2. Correlation between SLNB post-surgery and residual tumour burden in axilla; Timepoint(s): On completion of surgery
3. Disease Free Survival (DFS); Timepoint(s): After 5-years follow-up
4. Distant Disease Free Survival; Timepoint(s): After 5-years follow-up
5. Health Economics; Timepoint(s): After 2-years follow-up
6. Overall Survival; Timepoint(s): After 5-years follow-up
7. pCR rate in breast alone; Timepoint(s): After 4 cycles of NAC
8. Pharmacogenetic analysis to identify differences in toxicity and efficacy in individuals with spec; Timepoint(s): After 5-years follow-up

9. Quality of Life; Timepoint(s): After 2-years follow-up
10. Radiological response in breast alone; Timepoint(s): After 4 cycles of NAC
11. Rates of breast conservation; Timepoint(s): On completion of surgery
12. Sensitivity of Sentinal Lymph Node Biopsy (SLNB) following NAC in node positive patients; Timepoint(s): On completion of surgery
13. Time until loco-regional recurrence; Timepoint(s): After 5-years follow-up
14. Tolerability and toxicity of treatment; Timepoint(s): After 4 cycles of NAC
15. Utility of alternative molecular predictors of differential response to treatment; Timepoint (s): After 5 years follow-up

Overall study start date
01/07/2015

Completion date
31/05/2028

Eligibility

Key inclusion criteria
1. Patient with histological diagnosis of invasive breast cancer
2. Suitable for neo-adjuvant chemotherapy in opinion of investigator
3. Unifocal tumour: - Radiological size greater than or equal to (=) 20 mm by ultrasound (or in some cases Magnetic Resonance Imaging (MRI) is allowed)
4. T4 tumour of any size with direct extension to:
4.1. Chest wall
4.2. Skin
4.3. Both chest wall and skin
5. Inflammatory carcinoma with tumour of any size OR
6. Multifocal tumour: The sum of each tumour's maximum diameter must be =20 mm (total sum of multifocal deposits =20 mm by ultrasound) OR
7. Other locally advanced disease:
7.1. Biopsy confirmed axillary lymph node involvement or large or fixed axillary lymph nodes (radiological diameter =20 mm or clinical N2), or ipsilateral supraclavicular nodes and primary breast tumour of any diameter
7.2. - Involvement of large or fixed axillary lymph nodes (radiological diameter =20 mm or clinical N2), or ipsilateral supraclavicular nodes without a primary breast tumour identified: in this case the presence of breast cancer in a lymph node must be histopathologically confirmed by lymph node biopsy (trucut or whole lymph node)
8. Patients with bilateral disease are eligible to enter the trial, if one of the criteria above is met for disease in at least one breast
9. Any HER2 status
10. Patient fit to receive the trial chemotherapy regimen in the opinion of the responsible clinician. The following recommendations must be taken into account when making this assessment: Patients with HER2 positive disease must not have clinically significant cardiac abnormalities. Cardiac function should be assessed by physical examination and baseline measurement MUST be made of Left Ventricular Ejection Fraction (LVEF) by Multi Gated Acquisition (MUGA) scan or echocardiogram (ECHO). LVEF must be within the normal range as defined locally by the treating hospital. Patients must have adequate bone marrow, hepatic, renal and haematological function
11. Eastern Co-operative Oncology Group (ECOG) performance status of 0 or 1
12. Women of child-bearing potential, or men in a relationship with a woman of child-bearing

age, prepared to adopt adequate contraceptive measures if sexually active
13. 18 years or older
14. Male or female
15. Written informed consent for the trial
16. Availability of embedded paraffin tumour blocks from pre-chemotherapy biopsy is required
17. Willing and able to comply with scheduled visits, treatment plan and other study procedures
Sentinel Lymph Node Biopsy Study (in addition to above)
18. Biopsy/fine needle aspiration proven involved ipsilateral axillary lymph nodes at diagnosis

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 1050; UK Sample Size: 1050; Description: 1050 patients gives 90% power, 10% significance, for detecting an interaction. The power to test for an overall treatment effect regardless of CEP17/TOP2A status is >90%. Allowing for 10% loss to follow-up ensures >87% power to test for a treatment effect by CEP17/TOP2A interaction. The stratified approach has power to test for the interaction between CEP17/TOP2A status and treatment effect.

Total final enrolment
990

Key exclusion criteria
1. Tumours of low or intermediate grade (Grade 1 or 2) which are also Oestrogen Receptor (ER) rich and Progesterone Receptor (PgR) rich or PgR unknown, whatever the size or nodal status
2. Previous invasive breast cancer
3. Unequivocal evidence of metastatic disease
4. Previous diagnosis of other malignancy unless:
4.1. Disease- free for 5 years OR
4.2. Previous basal cell carcinoma, cervical carcinoma in situ, superficial bladder tumour OR
4.3. Contralateral or ipsilateral DCIS of the breast treated by surgery alone
5. Previous chemotherapy
6. Prior extensive radiotherapy (as judged by the investigator) to bone marrow
7. Previous neo-adjuvant endocrine therapy (unless less than 6 weeks duration)
8. Concomitant hormonal therapies/chemotherapy or any other medical treatment in relation to treating the breast cancer
9. In HER2 positive patients risk factors precluding co-administration of trastuzumab and FEC75
9.1. Previous myocardial infarction during the 6 months prior to recruitment
9.2 LVEF below institutional lower limit of normal and no echocardiographic evidence of haemodynamically
9.3 Significant valvular heart disease or ventricular contractility
10. Prior diagnosis of cardiac failure

11. Uncontrolled hypertension, coronary heart disease other significant cardiac abnormality
12. Bleeding diathesis
13. Presence of active uncontrolled infection
14. Any evidence of other disease which in the opinion of the investigator places the patient at high risk of treatment-related complication
15. Pregnant (female patients of childbearing potential should have a urine or blood Human Chorionic Gonadotropin test performed to rule out pregnancy prior to trial entry)
16. Lactating females
17. Any concomitant medical or psychiatric problems which in the opinion of the investigator would prevent completion of treatment or follow-up
18. Sentinel Lymph Node Biopsy Study (in addition to above)
19. Negative nodes at diagnosis
19. SLNB at diagnosis
20. Allergy to patent blue dye

Date of first enrolment
01/07/2015

Date of final enrolment
31/05/2023

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Cancer Research UK
Institute for Cancer Studies
University of Birmingham
Edgbaston
Birmingham
United Kingdom
B15 2TT

Sponsor information

Organisation
University of Birmingham

Sponsor details
Edgbaston
Birmingham
England

United Kingdom
B15 2TT
-
no@email.provided

Sponsor type
University/education

ROR
https://ror.org/03angcq70

Funder(s)

Funder type
Government

Funder Name
Cancer Research UK

Alternative Name(s)
CR_UK, Cancer Research UK - London, CRUK

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
United Kingdom

Funder Name
Celgene International Sarl (Switzerland)

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal a year after the last patient has completed their 5-year follow-up.

Intention to publish date
31/05/2029

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from the Cancer Research UK Clinical Trials Unit (CRCTU), University of Birmingham. Data will be shared in accordance with the CRCTUs data sharing policy which is available on the CRCTU website (https://www.birmingham.ac.uk/research/crctu/Data-sharing-policy.aspx). Anonymised data will be available 6 months after the publication of the outcome measures.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No