Trial Synopsis

**ROSCO:** Response to Optimal Selection of neo-adjuvant Chemotherapy in Operable breast cancer

**Chief Investigator** Daniel Rea

**Sponsor** University of Birmingham

**EudraCT No.** 2013-004307-39

**Trial Design**
A multicentre, phase III, randomised (1:1) biomarker stratified, open-label, clinical trial designed to answer the following questions:

1. Is there a role for CEP17/TOP2A testing in selecting anthracycline or taxane chemotherapy as neo-adjuvant chemotherapy for early breast cancer? Specifically does CEP17/TOP2A status predict differential efficacy of anthracycline or taxane based therapy as assessed by measurement of a statistically significant treatment-biomarker interaction?

2. Is Sentinel Lymph Node Biopsy (SLNB) post neo-adjuvant chemotherapy in patients with biopsy proven ipsilateral axillary lymph node metastasis at diagnosis sufficiently sensitive to replace routine axillary node clearance?

**Primary Outcome Measure**
- Complete pathological response (pCR) rate

**Main Secondary Outcome Measures**
- Rates of breast conservation
- Radiological response in breast alone
- Sensitivity of SLNB following neo-adjuvant chemotherapy
- Quality of Life
- Clinical response in breast alone
- Tolerability and toxicity of treatment
- Survival
- Health economics

**Population and Sample Size**
1050 patients with early operable breast cancer

**Main Eligibility Criteria**

**Inclusion**
- Patient with histological diagnosis of invasive breast cancer
- Suitable for neo-adjuvant chemotherapy
- Radiological size \( \geq 20 \) mm by ultrasound
- Suitable for and fit to receive protocol specified trial chemotherapy
- Any Human Epidermal Growth Factor Receptor 2 (HER2) status
- Availability of embedded paraffin tumour blocks from pre-chemotherapy biopsy is required

**Inclusion for the Sentinel Lymph Node Biopsy Protocol (in addition to the above)**
- Histopathological or cytological confirmation of involved nodes by biopsy/fine needle aspiration of ipsilateral axillary lymph nodes at diagnosis

**Exclusion**
- ‘Luminal A’ type tumours defined as tumours of low or intermediate grade (Grade 1 or 2), HER2 negative, which are also ER rich and progesterone receptor (PgR) rich or PgR unknown whatever the size or nodal status
- Previous breast cancer
- Unequivocal metastatic disease
- Uncontrolled hypertension, coronary heart disease, other significant cardiac abnormality
- Risk factors precluding co-administration of trastuzumab and FEC75

**Exclusion for the Sentinel Lymph Node Biopsy Protocol (in addition to the above)**
- Negative nodes at diagnosis
- SLNB at diagnosis
- Allergy to patent blue dye
Trial Summary

Trial Treatment:

**Arm A (Control):** 5-Fluorouracil 500mg/m², epirubicin 100mg/m², and cyclophosphamide 500mg/m² (FEC100)† 3 weekly x4 cycles ➔ surgery ➔ if pCR not achieved then docetaxel 75mg/m² and cyclophosphamide 600mg/m² 3 weekly x4 cycles.

**Arm B:** Docetaxel 75mg/m² and cyclophosphamide 600mg/m²† 3 weekly x4 cycles ➔ surgery ➔ if pCR not achieved then FEC100† 3 weekly x4 cycles.

After chemotherapy axillary node clearance +/- SLNB* will be mandatory in all patients with clinically or pathologically involved nodes prior to chemotherapy.

† All HER2 positive patients will receive Trastuzumab at 8mg/kg with first cycle of chemotherapy followed by 6mg/kg 3 weekly for 6-12 months. HER2 positive patients allocated to FEC will receive FEC75 (5-Fluorouracil 500mg/m², epirubicin 75mg/m², and cyclophosphamide 500mg/m² 3 weekly x4 cycles) to limit anthracycline exposure.

* SLNB required for patients taking part in the SLNB Study.

Tumour Samples

The following tumour samples are required:

- Tumour biopsy block pre-treatment for CEP17/TOP2A analysis
- Interim biopsy block post-treatment (if applicable) but prior to surgery
- Tumour block at surgery

Optional Sub-studies

- Quality of Life and health economics
- Pharmacogenetics

Trial Duration

- Recruitment: 5 years
- Treatment duration: 12-33 weeks
- Follow-up: 5 years

Contact Details

**ROSCO Trial Office**
Cancer Research UK Clinical Trials Unit (CRCTU), School of Cancer Sciences, University of Birmingham, Edgbaston, Birmingham. B15 2TT
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**CEP17/TOP2A Central Testing**
HER2 Team, Cellular Pathology, Heart of England NHS Foundation Trust, Bordesley Green East Birmingham. B9 5SS
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**Translational Coordinating Centres**

**Edinburgh (Tumour Blocks)**
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**Cambridge (Blood Samples)**
Caron Harvey, Cambridge Cancer Trials Centre, Cambridge Clinical Trials Unit - Cancer Theme, Cambridge University Hospitals NHS Foundation Trust, Box 279 (S4), Addenbrooke's Hospital, Cambridge Biomedical Campus, Hills Road, Cambridge. CB2 0QQ
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**Trial Schema**

**Identify Eligible Patients**
- Patient with histological diagnosis of invasive breast cancer
- Suitable for neo-adjuvant chemotherapy
- Radiological size ≥20 mm by ultrasound
- Suitable for and fit to receive protocol specified trial chemotherapy regimen
- Any HER2 status
- Availability of embedded paraffin tumour blocks from pre-chemotherapy biopsy is required

**Obtain Consent**
- Register Patient
  - Call ROSCO Trial Office on 0800 371 969

**Tissue sent for CEP17/TOP2A Analysis**

**Randomisation**
- Call ROSCO Trial Office on 0800 371 969
- CEP17/TOP2A status
- ER status
- HER2 status
- Nodal involvement

**Arm A: FEC**
- FEC100
  - 3 weekly X 4
  - All HER2 +ve patients to receive trastuzumab and FEC75

**Arm B: Taxane**
- Docetaxel and cyclophosphamide
  - 3 weekly X 4
  - All HER2 +ve patients to receive trastuzumab

**Surgery**
- (to include Sentinel Lymph Node Biopsy and Axillary Node Clearance (if Fine Needle Aspirate or biopsy positive at presentation)
- Assessment of Pathological Response (samples also sent for central review)

**Achieve Pathological Complete Response**
- Docetaxel and cyclophosphamide
  - 3 weekly X 4
  - All HER2 +ve patients to receive trastuzumab

**Failure to Achieve Response on FEC**
- FEC100
  - 3 weekly X 4
  - All HER2 +ve patients to receive trastuzumab and FEC75

**Failure to Achieve Response on Taxane**

**Follow-up For 5-years**
## Schedule of Events

<table>
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<th>Assessment</th>
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<th>Neo-adjuvant Chemotherapy Treatment</th>
<th>Protocol Defined Adjuvant Chemotherapy Treatment</th>
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<th>Follow-up</th>
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<td>After C4</td>
<td>On completion neo-adjuvant chemotherapy</td>
<td>Prior to d1 of each cycle</td>
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### Notes:
1. Except C1
2. A biopsy should be performed after C4 for patients who do not respond to chemotherapy and require crossover neo-adjuvant treatment
3. Only if clinically indicated
4. Only if cycle 4 is not last cycle
5. Left Ventricular Ejection Fraction (LVEF) must be measured for all Human Epidermal Growth Factor Receptor 2 (HER2) positive patients by echocardiogram (ECHO) or Multi Gated Acquisition (MUGA) scan. Modality used should be consistent throughout the study.
6. HER2 positive patients who are receiving/have received trastuzumab require cardiac monitoring with ECHO or MUGA as per institutional standard
7. Radiological tumour measurement of the breast, and assessment of ipsilateral axilla: Magnetic Resonance Imaging (MRI) may be used in addition to ultrasound in accordance with local practice, or as the sole radiological technique if the tumour is not measurable by another method
8. Uninformative baseline radiological assessments do not have to be repeated at later time points
9. Required for CEP17/TOP2A analysis prior to randomisation
10. Only for those few patients where the neo-adjuvant aim of down staging to permit breast conservation has not been achieved and the investigator considers that further chemotherapy provides a realistic prospect of achieving a successful down staging effect and thus an interim biopsy is taken after cycle 4.
11. Liver function tests: Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST), and Alkaline Phosphatase (ALP) and Bilirubin
12. Pregnancy test (Human Chorionic Gonadotropin urine or blood) should be performed if indicated at baseline for women of child bearing capacity
13. A full physical examination is not required at each clinic visit nor is clinical assessment of breast lesions unless there is concern or at discretion of the investigator
14. Only patients consenting to the Quality of Life and Health Economics Sub-study. Baseline QoL Questionnaire Booklets will handed out at clinic subsequent questionnaires will be sent from the ROSCO Trial Office
15. Only patients consenting to the Pharmacogenetics Translational Sub-study