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

A randomised phase III, stratified CEP17 biomarker trial of neo-adjuvant 5-Flourouracil, Epirubicin and Cyclophosphamide vs Docetaxel and Cyclophosphamide chemotherapy
Can we be smarter about who gets which chemotherapy drugs?
Collected all the blocks from sites
Failed to show that either of the proposed candidates—HER-2 amplification or TOPO II deletion/amplification drives sensitivity to epirubicin
Primary hypothesis not proven
Interim analysis: CEP17 & anthracycline benefit (OS) across 4 trials:

HR for interaction: 0.63 (0.46-0.86) p=0.0036; p = 0.026

Adjusted for treatment, nodes, grade, stage, HER2, TOP2A, CEP17, HER2*treatment and TOP2A* treatment. N = 2196.
FISH to detect amplification of HER-2
Worldwide metanalysis
CEP17 AND TOP2A contribute

Recurrence free survival

<table>
<thead>
<tr>
<th></th>
<th>Anth</th>
<th>CMF</th>
<th>Anth : CMF</th>
<th>Anth : CMF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events/Patients</td>
<td>ECMF</td>
<td>CMF</td>
<td>*Hazard Ratio &amp; CI</td>
</tr>
<tr>
<td>TOP2A/CEP17 Normal</td>
<td>319/902</td>
<td>324/892</td>
<td>0.95 (0.81, 1.11)</td>
<td></td>
</tr>
<tr>
<td>(35.4%)</td>
<td>(36.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOP2A Normal CEP17 Dup</td>
<td>88/254</td>
<td>149/307</td>
<td>0.66 (0.51, 0.85)</td>
<td></td>
</tr>
<tr>
<td>(34.6%)</td>
<td>(48.5%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOP2A Abnormal CEP17 Normal</td>
<td>52/144</td>
<td>57/116</td>
<td>0.61 (0.42, 0.90)</td>
<td></td>
</tr>
<tr>
<td>(36.1%)</td>
<td>(49.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOP2A Abnormal CEP17 Dup</td>
<td>58/138</td>
<td>98/166</td>
<td>0.59 (0.43, 0.81)</td>
<td></td>
</tr>
<tr>
<td>(42.0%)</td>
<td>(59.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stratified</td>
<td>517/1438</td>
<td>628/1481</td>
<td>0.79 (0.70, 0.89)</td>
<td></td>
</tr>
<tr>
<td>(36.0%)</td>
<td>(42.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity between 4 groups $\chi_3^2=12.1; P=.007$

* 95% CI  ← 95% CI

Bartlett et al JCO in Press
Association of pCR and outcomes (CT NeoBC metanalysis)

Event-free Survival

Overall Survival

pCR = ypT0/is ypN0

* Nominal p-value

Cortazar et al. SABCS 2012
NSABP B-27: Path. CR in Breast
Adding docetaxel doubles pCR

<table>
<thead>
<tr>
<th>Group</th>
<th>DCIS only</th>
<th>No Tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>3.7%</td>
<td>9.1%</td>
</tr>
<tr>
<td>II</td>
<td>18.9%</td>
<td>9.9%</td>
</tr>
<tr>
<td>III</td>
<td>4.4%</td>
<td>14.3%</td>
</tr>
</tbody>
</table>

Grp. I Grp. II Grp. III

26.1%* 12.8%* 14.3%*

*p<0.001 for test of heterogeneity across groups

n=764 n=767 n=775
Selecting drugs for chemotherapy in early breast cancer

- Potential markers for individual drug sensitivity have not been proven of benefit in prospective randomised trials
- Chemotherapy benefit from anthracyclines and taxanes appears to be distributed evenly across all standard prognostic parameters
- Age, size, grade, nodes, ER, PR, HER-2, etc
HER-2 positive will have concurrent trastuzumab in both arms FEC75 to be used for HER-2 positive otherwise use FEC 100
Abnormal nodes will be biopsied and those with biopsy proven node involvement will proceed to blue dye and isotope SLNBX and ALNC as a single stage procedure as part of their definitive surgery. A close rerun of ACOSOG Z1071 with better SLNB QA.
Primary Trial Questions

• Does a combination of either CEP-17 amplification or TOPOII abnormality select patients who will benefit more from taxane or anthracycline based initial chemotherapy?

• Is a negative sentinel node biopsy an accurate staging technique post neoadjuvant chemotherapy where there is preoperative histological confirmation of positive axillary nodes?
ROSCO: Cross over if no pCR achieved

Invasive breast cancer suitable for neoadjuvant chemotherapy

Randomised And Biomarker stratified

/docetaxel cyclo/

Surgery

FEC

D/C

FEC
B-27

Lumpectomy Rate

P = 0.33

AC

AC → Taxotere

Bear et al, JCO, Nov 15 2003
Presurgical crossover permitted in exceptional cases

Presurgical crossover will be permitted only if there is histological confirmation of residual cancer after 4 cycles of chemotherapy
ROSCO: further chemo permitted if over if pCR achieved

Invasive breast cancer suitable for neoadjuvant chemotherapy

Randomised And Biomarker stratified

FEC

DOCETAXEL CYCLO

FEC

Surgery

TC
Inclusion Criteria

Inclusion criteria

• 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 neo-adjuvant 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)

• Biopsy/fine needle aspiration proven involved ipsilateral axillary lymph nodes at diagnosis
Exclusion Criteria

Exclusion criteria

• Tumours <20mm in absence of histologically confirmed malignant or large (total radiological tumour size ≥20mm) or fixed axillary or ipsilateral supraclavicular fossa nodes
• Tumours of low or intermediate grade (Grade 1 or 2) which are also ER rich and progesterone receptor (PgR) rich or PgR unknown whatever the size or nodal status
• Previous breast cancer
• 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
Association of pCR with event free survival
HER-2 Negative Hormone receptor positive

Cortazar et al. Lancet Oncology 2013
Some More Specific details

- Grade I or II ER rich PR rich HER-2 negative cases not eligible

- HER-2 positive cases eligible and receive concurrent trastuzumab but FEC75 not FEC 100 if randomised to FEC

- NHS England are funding Pertuzumab in first 4 neoadjuvant cycles only.
Sample size

- The intent is to recruit 1050 patients overall into the trial with a 1:1 allocation between taxane and anthracycline randomisation.

- Current sample size calculation based on CEP-17 amplification rates

- Assumptions regarding prevalence of CEP-17 and TOPOII abnormalities and proportion of HER-2 positives included will need to be monitored during recruitment phase with potential to adjust sample size downwards.
Primary outcome measure

pCR in breast and axilla. (ypTo/isN0)
Sample size based on Simon’s design for a prospective, phase III, stratified biomarker trial with a binary endpoint, testing for a differential treatment effect between CEP17N patients and CEP17D patients.

Assumptions: CEP17 amplification prevalence is 30%, HER2 positive patients will account for 15% of patients randomised, CEP17D within HER2 positive population will be 37%, pCR rate in CEP17N, HER2 negative patients is 20%, HER2 positive patients 35%, CEP17D, HER2 negative patients treated with anthracyclines 50% and CEP17D, HER2 positive patients treated with anthracyclines 65%.
Secondary outcome measures

- Rates of breast conservation
- Tolerability and toxicity of treatment
- Sensitivity of SLNB following neo-adjuvant chemotherapy
- Survival
- Quality of Life
- Utility of alternative molecular predictors
- Health Economics
- Pharmacogenetics
Tumour samples

The following tumour samples are required:

• Tumour biopsy block pre-treatment for CEP17 analysis

• Interim biopsy block post treatment (if applicable) but prior to surgery

• Tumour block at surgery

• Frozen tumour cores if contributing to detailed translational component
Trial management Committee

Daniel Rea (Chief Investigator)
Larry Hayward (Deputy Chief Investigator)
Adele Francis (Surgery)
Jeremy Thomas (Pathology)
John Bartlett (Translational Pathology)
Andrew Stanley (Pharmacy)
David Cameron, Trevor McGoldrick, Robert Stein, Helena Earl (Oncology)
Jean Abraham, (Pharmacogenomics)
Jane Starczynski (Biomarker Assays)
Cassandra Brookes (Statistics)
Emma Frew (Health Economics)
Sarah Bowden (Senior Trial Coordinator)
Phillipa Treharne-Jones (Trial Coordinator)
Muraid Mckenzie (PPI)
Open sites

- England
- Alexandra Hospital, Redditch
- Chesterfield Royal Hospital
- City Hospital, Birmingham
- George Eliot Hospital
- Huddersfield Royal Infirmary
- Kidderminster General Hospital
- Macclesfield General Hospital
- Medway Hospital
- Musgrove Park Hospital
- Nottingham City Hospital
- Norfolk and Norwich University Hospital
- Peterborough City Hospital
- Queen Elizabeth Hospital, Birmingham
- Rotherham Hospital
- Royal Cornwall Hospital
- Royal Bournemouth Hospital
- University Hospital Coventry
- University Hospital North Tees
- Weston Park Hospital
- Worcester Royal Hospital
- Yeovil District Hospital
Open sites (cont.)

Scotland
Beatson West of Scotland Cancer Care
Borders General Hospital
Dumfries and Galloway Royal Infirmary
Forth Valley Royal Hospital
New Victoria Infirmary, Glasgow
University Hospital Crosshouse
University Hospital Ayr
Western General Hospital, Edinburgh
## Recruitment by site

<table>
<thead>
<tr>
<th>Site</th>
<th>Pts</th>
<th>Site</th>
<th>Pts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queen Elizabeth Hospital, Birmingham</td>
<td>25</td>
<td>Victoria Infirmary</td>
<td>3</td>
</tr>
<tr>
<td>Royal Bournemouth Hospital</td>
<td>22</td>
<td>Royal Cornwall Hospital</td>
<td>2</td>
</tr>
<tr>
<td>Peterborough City Hospital</td>
<td>12</td>
<td>University Hospital North Tees</td>
<td>2</td>
</tr>
<tr>
<td>Yeovil Hospital</td>
<td>12</td>
<td>University Hospital Coventry</td>
<td>2</td>
</tr>
<tr>
<td>Nottingham City Hospital</td>
<td>11</td>
<td>Royal Cornwall Hospital</td>
<td>2</td>
</tr>
<tr>
<td>Weston Park Hospital</td>
<td>10</td>
<td>Macclesfield General Hospital</td>
<td>2</td>
</tr>
<tr>
<td>Western General Hospital</td>
<td>8</td>
<td>Medway Hospital</td>
<td>1</td>
</tr>
<tr>
<td>Norfolk and Norwich University Hospital</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Recruitment (cumulative)
Further Information

Phillipa Treharne-Jones
CRCTU Birmingham
PJ.Jones@bham.ac.uk
0121 414 3921
• The sensitivity rate of SLNB at identifying macrometastases will need to be at approximately 90% to be acceptable to surgeons and patients and similar to that in patients unexposed to systemic therapy.

• We estimate 24% with lymph nodal involvement. Approximately 252 patients will be available for analysis to determine the sensitivity of SLNB compared to an axillary clearance, of which approximately 202 (80%) will have nodal involvement as assessed by an axillary clearance based on an overall pCR rate of 20%.

• If SLNB correctly predicts nodal involvement in at least 90% of cases. And the true sensitivity was around 95%, 202 patients would provide enough patients to ensure the lower confidence limit did not fall below the lowest acceptable level of sensitivity (90%), approximately 90% of the time.
Paradoxical good residual risk in AC-T CEP17 abnormal vs normal 17?
CEP17 probe detects a pericentromeric alpha satellite repeat of no known function.
DBCG 07-READ
A randomized phase III trial comparing six cycles of docetaxel and cyclophosphamide (DC) to three cycles of epirubicin and cyclophosphamide followed by three cycles of docetaxel (EC-D) in patients with early breast cancer

for the Danish Breast Cancer Cooperative Group (DBCG)
**DBCG 07- READ trial design**

**Selection Criteria**
- Invasive breast cancer
- Comorbidity index < 3
- High risk
  1. Node positive
  2. High risk node neg.
     - Young age
     - ER negative
     - HER2+
     - T size
     - High grade

**Altered TOP2A**
- TOP2A/Cen17 ratio < 0.8 or ≥ 2.0

3 x EC
- 90/600 mg/m²
- 100 mg/m²

3 x Docetaxel

**Normal TOP2A**
- TOP2A/Cen17 ratio 0.8-1.9

3 x EC
- 90/600 mg/m²
- 100 mg/m²

6 x DC
- 75/600 mg/m²
San Antonio Breast Cancer Symposium - December 6-10, 2016

Results; DFS and OS

Disease Free Survival (%)

HR = 1.00 95% CI (0.78;1.26), P = 1.00

Overall Survival (%)

HR = 1.15 95% CI (0.83;1.59), P = 0.41

This presentation is the intellectual property of the author/presenter. Contact be@dbcq.dk for permission to reprint and/or distribute.
### Results: subgroup analysis

**Disease-free survival**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>HR</th>
<th>95% - CI</th>
<th>Favors DC</th>
<th>Favors EC-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Size (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–20</td>
<td>1197</td>
<td>0.97</td>
<td>(0.68 - 1.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21+</td>
<td>815</td>
<td>1.03</td>
<td>(0.76 - 1.39)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen Receptor Status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>572</td>
<td>1.01</td>
<td>(0.71 - 1.44)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10+</td>
<td>1440</td>
<td>1.00</td>
<td>(0.72 - 1.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>335</td>
<td>1.89</td>
<td>(0.90 – 4.00)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>912</td>
<td>1.40</td>
<td>(0.96 – 2.05)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>639</td>
<td>0.70</td>
<td>(0.49 – 0.99)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KI67 (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–14</td>
<td>632</td>
<td>1.20</td>
<td>(0.77 – 1.89)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;14</td>
<td>1156</td>
<td>0.96</td>
<td>(0.72 – 1.28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1052</td>
<td>0.77</td>
<td>(0.54 – 1.11)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>960</td>
<td>1.29</td>
<td>(0.91 – 1.82)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2012</td>
<td>1.01</td>
<td>(0.79 – 1.29)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Overall survival**

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>HR</th>
<th>95% - CI</th>
<th>Favors DC</th>
<th>Favors EC-D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor Size (mm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–20</td>
<td>1197</td>
<td>1.29</td>
<td>(0.79 – 2.10)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21+</td>
<td>815</td>
<td>1.12</td>
<td>(0.77 – 1.65)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estrogen Receptor Status (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–9</td>
<td>572</td>
<td>1.11</td>
<td>(0.72 – 1.71)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10+</td>
<td>1440</td>
<td>1.27</td>
<td>(0.79 – 2.03)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malignancy Grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>335</td>
<td>1.62</td>
<td>(0.56 – 5.93)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>912</td>
<td>1.94</td>
<td>(1.13 – 3.30)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>639</td>
<td>0.79</td>
<td>(0.51 – 1.24)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KI67 (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0–14</td>
<td>632</td>
<td>1.54</td>
<td>(0.82 – 2.88)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;14</td>
<td>1156</td>
<td>1.15</td>
<td>(0.78 – 1.67)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Menopausal Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre</td>
<td>1052</td>
<td>0.85</td>
<td>(0.53 – 1.37)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post</td>
<td>960</td>
<td>1.57</td>
<td>(1.00 – 2.47)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>2012</td>
<td>1.18</td>
<td>(0.85 – 1.63)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Hazard Ratio**

<table>
<thead>
<tr>
<th>0.5</th>
<th>1.0</th>
<th>2.0</th>
<th>4.0</th>
</tr>
</thead>
</table>

This presentation is the intellectual property of the author/presenter. Contact be@dbraco.dk for permission to reprint and/or distribute.