



# Anastrozole versus tamoxifen for the prevention of locoregional and contralateral breast cancer in postmenopausal women with locally excised ductal carcinoma in situ (IBIS-II DCIS): a double-blind, randomised controlled trial



John F Forbes, Ivana Sestak, Anthony Howell, Bernardo Bonanni, Nigel Bundred, Christelle Levy, Gunter von Minckwitz, Wolfgang Eiermann, Patrick Neven, Michael Stierer, Chris Holcombe, Robert E Coleman, Louise Jones, Ian Ellis, Jack Cuzick, on behalf of the IBIS-II investigators\*

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\*Members listed in appendix

Australia and New Zealand Breast Cancer Trials Group, University of Newcastle, Waratah, NSW, Australia (Prof J F Forbes MD); Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine (I Sestak PhD, Prof J Cuzick PhD) and Barts Cancer Institute (Prof L Jones PhD), Queen Mary University of London, London, UK; Genesis Breast Cancer Prevention Centre, Manchester, UK (Prof A Howell MD); Division of Cancer Prevention and Genetics, European Institute of Oncology, Milan, Italy (B Bonanni MD); South Manchester University Hospital, Manchester, UK (Prof N Bundred MD); Centre François Baclesse, Caen, France (C Levy MD); German Breast Group, Frankfurt, Germany (Prof G von Minckwitz MD); Interdisziplinäres Onkologisches Zentrum, Munich, Germany (W Eiermann MD); Department of Oncology, KU Leuven, University of Leuven, Leuven, Belgium (Prof P Neven MD); Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria (Prof M Stierer MD); Linda McCartney Centre, Royal Liverpool University Hospital, Liverpool, UK (C Holcombe MD); Department of Oncology and Metabolism, Weston Park Hospital, Sheffield, UK (Prof R E Coleman MD); and Department of Histopathology, University of Nottingham, Nottingham, UK (Prof I Ellis MD)

## Summary

**Background** Third-generation aromatase inhibitors are more effective than tamoxifen for preventing recurrence in postmenopausal women with hormone-receptor-positive invasive breast cancer. However, it is not known whether anastrozole is more effective than tamoxifen for women with hormone-receptor-positive ductal carcinoma in situ (DCIS). Here, we compare the efficacy of anastrozole with that of tamoxifen in postmenopausal women with hormone-receptor-positive DCIS.

**Methods** In a double-blind, multicentre, randomised placebo-controlled trial, we recruited women who had been diagnosed with locally excised, hormone-receptor-positive DCIS. Eligible women were randomly assigned in a 1:1 ratio by central computer allocation to receive 1 mg oral anastrozole or 20 mg oral tamoxifen every day for 5 years. Randomisation was stratified by major centre or hub and was done in blocks (six, eight, or ten). All trial personnel, participants, and clinicians were masked to treatment allocation and only the trial statistician had access to treatment allocation. The primary endpoint was all recurrence, including recurrent DCIS and new contralateral tumours. All analyses were done on a modified intention-to-treat basis (in all women who were randomised and did not revoke consent for their data to be included) and proportional hazard models were used to compute hazard ratios and corresponding confidence intervals. This trial is registered at the ISRCTN registry, number ISRCTN37546358.

**Results** Between March 3, 2003, and Feb 8, 2012, we enrolled 2980 postmenopausal women from 236 centres in 14 countries and randomly assigned them to receive anastrozole (1449 analysed) or tamoxifen (1489 analysed). Median follow-up was 7·2 years (IQR 5·6–8·9), and 144 breast cancer recurrences were recorded. We noted no statistically significant difference in overall recurrence (67 recurrences for anastrozole vs 77 for tamoxifen; HR 0·89 [95% CI 0·64–1·23]). The non-inferiority of anastrozole was established (upper 95% CI <1·25), but its superiority to tamoxifen was not ( $p=0·49$ ). A total of 69 deaths were recorded (33 for anastrozole vs 36 for tamoxifen; HR 0·93 [95% CI 0·58–1·50],  $p=0·78$ ), and no specific cause was more common in one group than the other. The number of women reporting any adverse event was similar between anastrozole (1323 women, 91%) and tamoxifen (1379 women, 93%); the side-effect profiles of the two drugs differed, with more fractures, musculoskeletal events, hypercholesterolaemia, and strokes with anastrozole and more muscle spasm, gynaecological cancers and symptoms, vasomotor symptoms, and deep vein thromboses with tamoxifen.

**Conclusions** No clear efficacy differences were seen between the two treatments. Anastrozole offers another treatment option for postmenopausal women with hormone-receptor-positive DCIS, which may be more appropriate for some women with contraindications for tamoxifen. Longer follow-up will be necessary to fully evaluate treatment differences.

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## Introduction

Breast cancer is the most common cancer in women worldwide, with an estimated 1·6 million new cases reported every year.<sup>1</sup> The proportion of these that are diagnosed as ductal carcinoma in situ (DCIS) has substantially increased over the past few decades due to

the introduction of mammographic screening. It is estimated that approximately a fifth of all screen-detected breast cancers are DCIS.<sup>2</sup>

Management strategies for DCIS vary depending on histological grade, tumour characteristics, and extent of disease. Almost all aspects of treatment are controversial,

## Research in context

### Evidence before this study

A PubMed search between Jan 1, 1990, and Dec 31, 2002 (with the terms “ductal carcinoma in situ”, “breast cancer”, “aromatase inhibitors”, and “endocrine therapy”) and discussion with colleagues yielded no clinical trials or large cohorts of women with ductal carcinoma in situ (DCIS) treated by aromatase inhibitors. There have been two previous trials of tamoxifen. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial, all women with DCIS received radiotherapy before being randomly assigned to tamoxifen or matching placebo. After a median of 6 years of follow-up, a significant 37% reduction in breast cancer recurrence was observed with tamoxifen compared with placebo. In the UK/ANZ DCIS trial, 1578 women with locally excised DCIS were randomly assigned to receive tamoxifen with or without radiotherapy. After a median of 12·7 years of follow-up, tamoxifen significantly reduced all new breast cancer events by 29%, with a significant effect on ipsilateral DCIS recurrence and contralateral tumours, but no effect on ipsilateral invasive recurrence. A further PubMed search was performed in October, 2015, which found no further published articles except the NSABP B-35 trial conference abstract.

### Added value of this study

In combination with the B-35 trial, this trial provides the first evidence for the use of an aromatase inhibitor (here, anastrozole) compared with tamoxifen for postmenopausal women with locally excised hormone-receptor-positive DCIS after a median follow-up of 7·1 years. In this study, no clear efficacy differences were seen between the two treatments, although all available evidence supports a greater efficacy for anastrozole.

### Implications of all the available evidence

Our results are consistent with the small benefit of anastrozole versus tamoxifen as seen in the NSABP B-35 trial. This is also supported by direct evidence of greater efficacy for recurrence in adjuvant trials of women with early invasive cancer and indirect evidence of greater efficacy against new cancers in a preventive setting. Side-effect profiles between the drugs differed, but there was no clear overall advantage for either treatment. Anastrozole offers another treatment option for postmenopausal women with oestrogen-receptor-positive DCIS which might be more appropriate for some women with contraindications to tamoxifen.

Correspondence to:  
Prof Jack Cuzick, Centre for  
Cancer Prevention, Wolfson  
Institute of Preventive Medicine,  
Charterhouse Square,  
London EC1M 6BQ, UK  
[j.cuzick@qmul.ac.uk](mailto:j.cuzick@qmul.ac.uk)

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including the need for any treatment for some screen-detected lesions,<sup>3</sup> the extent of surgery,<sup>4</sup> the use of radiotherapy,<sup>5,6</sup> and the use of adjuvant endocrine therapy.<sup>7,8</sup> The role of tamoxifen has been investigated in two large trials.<sup>7,8</sup> In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-24 trial,<sup>7</sup> all women with DCIS received radiotherapy before being randomly assigned to tamoxifen or matching placebo. After a median of 6 years of follow-up, a significant 37% reduction in breast cancer recurrence was observed with tamoxifen compared with placebo.<sup>7</sup> Retrospective evaluation of oestrogen receptors (ER) and progesterone receptors (PgR) in 732 patients from the original study showed that tamoxifen reduced subsequent breast cancer events by 51% for women with ER-positive DCIS.<sup>9</sup> However, no significant benefit with tamoxifen was observed for women with ER-negative DCIS. In the UK/ANZ DCIS trial,<sup>8</sup> 1578 women with locally excised DCIS were randomly assigned to receive tamoxifen with or without radiotherapy. After a median of 12·7 years of follow-up, tamoxifen significantly reduced all new breast cancer events by 29%, with a significant impact on ipsilateral DCIS recurrence and contralateral tumours, but no effect on ipsilateral invasive recurrence.<sup>8</sup>

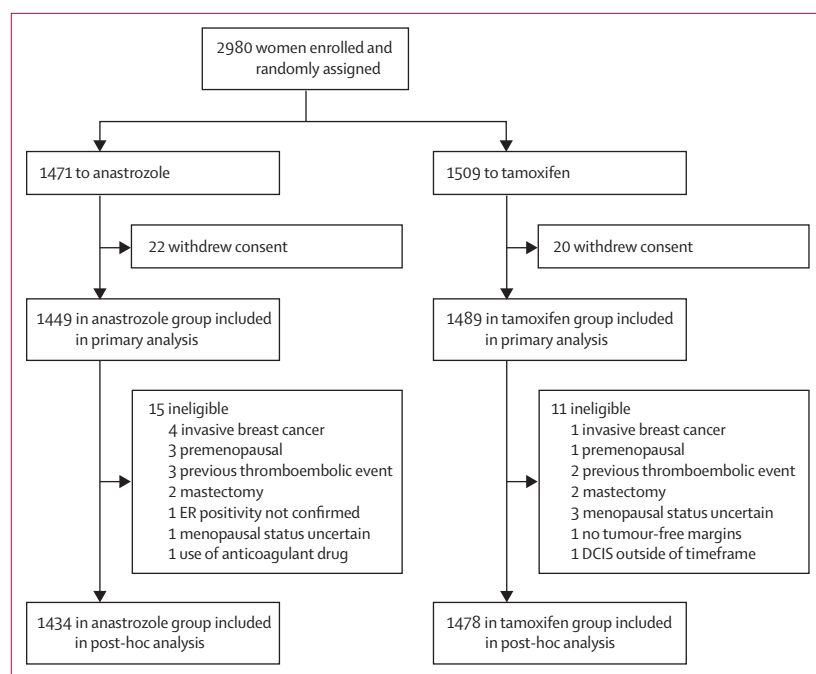
Until now no data have been available on the use of aromatase inhibitors for DCIS. Two trials of very similar design have been conducted. Both compared anastrozole with tamoxifen in postmenopausal women with ER-positive or PgR-positive DCIS. The NSABP B-35 results will be reported elsewhere.<sup>10</sup> Here, we report the first results from the International Breast Cancer Intervention Study-II DCIS (IBIS-II DCIS).

## Methods

### Study design and participants

We undertook a double-blind, randomised, placebo-controlled trial to compare anastrozole with tamoxifen for the prevention of locoregional and contralateral breast cancer. Participants were women aged 40–70 years, postmenopausal, and had DCIS diagnosed within 6 months before randomisation. Microinvasion of less than 1 mm was permitted. Patients treated by mastectomy were not eligible for this study but could be included in the IBIS-II breast cancer prevention trial.<sup>11</sup> Radiotherapy was permitted according to local practice. Margin status was determined by the local pathologist and ER and PgR positivity was determined as greater than or equal to 5% positive cells (equivalent of Quick-score of three or above and H-score of ten or above). After a protocol amendment on Feb 24, 2009, women were also allowed to enter the trial if they had been diagnosed with atypical hyperplasia or lobular carcinoma in situ to allow treatment of these benign breast diseases known to respond to tamoxifen.<sup>12,13</sup>

Exclusion criteria were: premenopausal at diagnosis; any previous diagnosis of breast cancer (including DCIS excised more than 6 months before randomisation or treated by mastectomy); diagnosis of any other cancer in the past 5 years (excluding non-melanoma skin cancer or in-situ cervical cancer); current treatment with anti-coagulants; previous diagnosis of deep-vein thrombosis, transient ischaemic attack, or cerebrovascular accident; previous or current use of selective oestrogen receptor modulators; intention to use menopausal hormone therapy; unexplained postmenopausal bleeding; evidence



**Figure 1: Trial profile**

ER=oestrogen receptor. DCIS=ductal carcinoma in situ.

|                                | Anastrozole (n=1449) | Tamoxifen (n=1489) |
|--------------------------------|----------------------|--------------------|
| Age, years                     | 60.4 (56.4–64.5)     | 60.3 (55.8–64.5)   |
| BMI, kg/m <sup>2</sup>         | 26.7 (23.5–30.4)     | 26.7 (23.7–30.2)   |
| Age at menarche, years         | 13.0 (12.0–14.0)     | 13.0 (12.0–14.0)   |
| Age at birth of first child    | 24.0 (21.0–27.0)     | 24.0 (21.0–27.0)   |
| Smoking                        |                      |                    |
| Never                          | 890 (61%)            | 934 (63%)          |
| Ever                           | 496 (34%)            | 495 (33%)          |
| Missing                        | 63 (4%)              | 60 (4%)            |
| Menopausal hormone therapy use | 678 (47%)            | 658 (44%)          |
| Hysterectomy                   | 406 (21%)            | 408 (22%)          |
| Radiotherapy                   | 1027 (71%)           | 1064 (71%)         |
| Tumour size, mm                | 13 (7–22)            | 13 (7–22)          |
| Margins, mm                    | 5 (2–10)             | 5 (2–10)           |
| Grade                          |                      |                    |
| Low                            | 293 (20%)            | 279 (19%)          |
| Intermediate                   | 606 (42%)            | 618 (42%)          |
| High                           | 542 (37%)            | 587 (39%)          |
| Missing                        | 8 (<1%)              | 5 (<1%)            |
| Laterality                     |                      |                    |
| Left                           | 742 (51%)            | 789 (53%)          |
| Right                          | 703 (49%)            | 696 (47%)          |
| Bilateral                      | 5 (<1%)              | 4 (<1%)            |

Data are median (IQR) or n (%). Characteristics given for the modified intention-to-treat population; numbers of individuals do not add to totals because of missing values. BMI=body-mass index.

**Table 1: Baseline demographic and tumour characteristics according to treatment allocation**

both; or life expectancy judged by the clinician to be less than 10 years.

All women provided written informed consent and the study was approved by the ethics committees of all participating institutions. The study sponsor was Queen Mary University of London.

### Randomisation and masking

Participants were randomly assigned in a 1:1 ratio to receive 1 mg/day oral anastrozole or 20 mg/day oral tamoxifen. Randomisation was stratified by major centre or hub. Randomised blocks (six, eight, or ten) were used to maintain balance and randomisation was performed centrally by electronic contact with the main trials centre. All treatment was given on a daily basis for 5 years and all women took two tablets per day (tamoxifen and anastrozole placebo, or anastrozole and tamoxifen placebo). All IBIS-II DCIS personnel, participants, and clinicians were masked to treatment allocation, except for the IBIS-II DCIS trial statistician, who had access to unblinded data, and the independent data monitoring committee, who reviewed interim data for safety purposes.

### Procedures

A dual-energy x-ray absorptiometry scan within 2 years before entry to the trial and two lateral spinal radiographs were required to assess bone density and vertebral fractures. Women were seen at 6 months, 12 months, and then annually up to the 5 year follow-up point at local clinics. Adherence to treatment was ascertained at each follow-up visit. After 5 years, follow-up was annual and either by a short postal questionnaire or clinic visit, depending on country. Clinical adverse events were recorded during the post-treatment follow-up period. Mammograms were performed at least every 2 years. Blood samples were taken at baseline, year 1, and year 5 for the evaluation of potential biomarkers.

### Outcomes

The primary endpoint of this analysis was the development of histologically confirmed breast cancer, both invasive and new or recurrent DCIS. First events were further categorised as local recurrence (all ipsilateral disease), distant recurrence (including node-positive contralateral disease and recurrences at distant sites [eg, lung, bone, etc]), or isolated contralateral events. Secondary endpoints included ER status, breast cancer mortality, other cancers, cardiovascular disease, fractures, adverse events, and non-breast cancer deaths. Prespecified subgroup analyses of recurrence were for invasive versus DCIS, contralateral versus ipsilateral, and ER status (ER positive vs ER negative); other subgroup analyses were exploratory. Further post-hoc analyses included PgR and HER2 receptor status for invasive recurrence only. Future plans are to explore outcomes by ER levels and HER2 status of the primary tumour when tissue collection is complete, and to

of severe osteoporosis (T-score less than −4 at total hip or lumbar spine or more than two fragility fractures); history of lactose intolerance, glucose intolerance, or

examine timing effects of treatment after the initial 5 year treatment period is completed.

### Statistical analysis

All analyses were done on a modified intention-to-treat basis, including all women who were enrolled, randomly assigned, and did not revoke consent for use of their data. Analyses of the efficacy endpoints were based on hazard ratios (HRs). Cox proportional hazard models<sup>14,15</sup> were used to derive these with corresponding 95% CIs. The analysis plan first tested non-inferiority of anastrozole (upper 95% CI of HR <1.25) and, if successful, then for the superiority of anastrozole. Survival curves were estimated using the Kaplan-Meier method.<sup>16</sup> Secondary endpoints were compared using odds ratios (ORs), which closely approximate relative risk for rare events. Adverse events are presented if predefined or occurred in at least 5% of participants, and Fisher's exact tests were used to compare adverse events when appropriate. Adherence was calculated using the Kaplan-Meier method, censoring at breast cancer recurrence, death, or 5 years of follow-up. All p values were two-sided.

We estimated a required sample size of 4000 on the basis of a 1.6% annual recurrence rate for tamoxifen-treated patients with a 16.7% relative reduction for anastrozole to show non-inferiority, and a 33% reduction to show superiority with 5-year median follow-up. Recruitment to the trial closed on Feb 8, 2012, after enrolment of 2980 of the 4000 planned participants. During the course of the trial, local recurrences occurred at less than half the rate anticipated in the analysis plan, due largely to improvements in the surgical treatment of DCIS. Consequently, the required numbers of events anticipated in the protocol would not be reached for a number of years, and the IBIS-II steering committee, with the agreement of the independent data monitoring committee, took the decision to analyse and report the results at this stage; data were collected up to the cutoff date of Sept 30, 2015.

All analyses were done using Stata version 13.1. This trial is registered at the ISRCTN registry, number ISRCTN37546358.

### Role of the funding source

The study funders had no role in design, data collection, data analysis, data interpretation, or writing of the report. IS had full access to all data in the study, and JC, JFF, and AH had final responsibility for the decision to submit for publication.

### Results

Between March 6, 2003, and Feb 8, 2012, we recruited 2980 postmenopausal women with locally excised ER-positive or PgR-positive DCIS in 236 centres from 14 countries, and randomly assigned them to receive anastrozole (n=1471) or tamoxifen (n=1509; figure 1). A

|               | Anastrozole<br>(n=1449) | Tamoxifen<br>(n=1489) | Unadjusted analysis |         | Adjusted analysis* |         |
|---------------|-------------------------|-----------------------|---------------------|---------|--------------------|---------|
|               |                         |                       | HR (95% CI)         | p value | HR (95% CI)        | p value |
| All           | 67 (5%)                 | 77 (5%)               | 0.89 (0.64–1.23)    | 0.49    | 0.83 (0.59–1.18)   | 0.31    |
| Invasive†     | 37 (3%)                 | 47 (3%)               | 0.80 (0.52–1.24)    | 0.32    | 0.72 (0.46–1.14)   | 0.16    |
| Ipsilateral   | 20 (1%)                 | 22 (1%)               | 0.93 (0.51–1.71)    | 0.82    | 0.77 (0.40–1.48)   | 0.44    |
| Contralateral | 17 (1%)                 | 25 (2%)               | 0.69 (0.37–1.28)    | 0.24    | 0.68 (0.36–1.29)   | 0.24    |
| DCIS          | 29 (2%)                 | 30‡ (2%)              | 0.99 (0.60–1.65)    | 0.98    | 0.98 (0.57–1.69)   | 0.95    |
| Ipsilateral   | 21 (1%)                 | 23 (2%)               | 0.94 (0.52–1.69)    | 0.83    | 1.03 (0.55–1.91)   | 0.93    |
| Contralateral | 8 (<1%)                 | 6 (<1%)               | 1.37 (0.47–3.94)    | 0.56    | 1.02 (0.33–3.18)   | 0.97    |

DCIS=ductal carcinoma in situ. HR=hazard ratio. \*Adjusted for age, body-mass index, menopausal hormone therapy, grade, margins, and radiotherapy. †1 missing for invasiveness. ‡1 missing data for laterality.

**Table 2: All breast cancer, invasive, and DCIS recurrences according to treatment allocation**

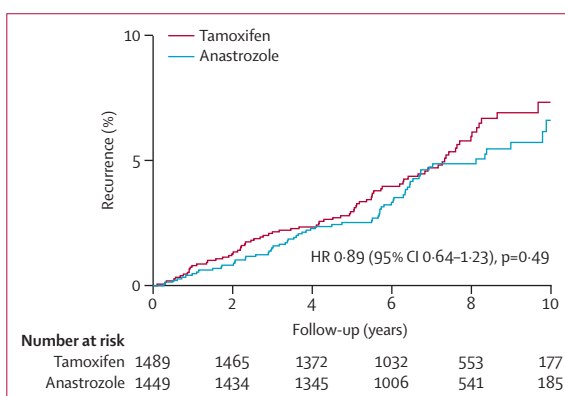


Figure 2: Recurrence for all breast cancer according to treatment allocation

total of 42 women (22 in the anastrozole group, 20 in the tamoxifen group) withdrew their consent to use their data, leaving 2938 women for the primary analysis (figure 1). Baseline characteristics are presented in table 1. A further 26 women were found to be ineligible after randomisation (figure 1) but were included in the primary analysis. Median age was 60.3 years (IQR 56.1–64.6), and 658 (22%) were older than 65 years. Median body-mass index was 26.7 kg/m<sup>2</sup> (IQR 23.6–30.4), with 903 (31%) of women being obese (>30 kg/m<sup>2</sup>) at baseline (table 1). Median age at menarche was 13 years (IQR 12–14) and at birth of first child was 24 years (IQR 21–27), and 814 (28%) women had had a hysterectomy before trial entry. 1336 (45%) women had used menopausal hormone therapy before trial entry and two-thirds were never-smokers (table 1). Only nine women (<1%) with atypical hyperplasia or lobular carcinoma in situ were entered into the trial.

Baseline DCIS tumour characteristics are also shown in table 1. Median DCIS major diameter was 13 mm (IQR 7–22), median clear margin distance was 5 mm (IQR 2–10), and most women had either intermediate-grade (1224; 42%) or high-grade (1129; 38%) tumours. Radiotherapy was given to 2091 (71%) women. Again, we noted no significant differences between treatment groups.

|                       | Anastrozole<br>(n=1449) | Tamoxifen<br>(n=1489) | OR (95% CI)        | p value |
|-----------------------|-------------------------|-----------------------|--------------------|---------|
| Total                 | 61                      | 71                    | 0.88 (0.61–1.26)   | 0.47    |
| Gynaecological        | 1                       | 17*                   | 0.06 (0.001–0.386) | 0.0002  |
| Endometrial           | 1                       | 11                    | 0.09 (0.002–0.64)  | 0.0044  |
| Ovarian               | 0                       | 5                     | 0.00 (0.00–0.79)   | 0.027   |
| Lung                  | 11                      | 7                     | 1.62 (0.57–4.94)   | 0.32    |
| Gastrointestinal      | 16                      | 10                    | 1.65 (0.70–4.08)   | 0.21    |
| Colorectal            | 10                      | 5                     | 2.06 (0.64–7.71)   | 0.18    |
| Lymphoma or leukaemia | 8                       | 5                     | 1.65 (0.47–6.42)   | 0.44    |
| Skin                  | 12                      | 23                    | 0.53 (0.24–1.12)   | 0.07    |
| Melanoma              | 4                       | 4                     | 1.03 (0.19–5.53)   | 0.97    |
| Non-melanoma          | 8                       | 19                    | 0.43 (0.16–1.03)   | 0.040   |
| Other                 | 13                      | 9                     | 1.49 (0.59–3.96)   | 0.36    |

OR=odds ratio. \*One cervical cancer.

**Table 3: Frequency of cancers other than breast according to treatment allocation**

|   | Anastrozole<br>(n=1449) | Tamoxifen<br>(n=1489) | OR (95% CI)       | p value |
|---|-------------------------|-----------------------|-------------------|---------|
| Fractures   | 129 (9%)                | 100 (7%)              | 1.36 (1.03–1.80)  | 0.027   |
| Pelvic or hip                                     | 11 (1%)                 | 4 (<1%)               | 2.84 (0.84–12.25) | 0.06    |
| Spine   | 6 (<1%)                 | 6 (<1%)               | 1.03 (0.27–3.85)  | 0.96    |
| Musculoskeletal (any)                             | 929 (64%)               | 811 (54%)             | 1.49 (1.28–1.74)  | <0.0001 |
| Arthralgia  | 832 (57%)               | 729 (49%)             | 1.41 (1.21–1.63)  | <0.0001 |
| Joint stiffness                                   | 74 (5%)                 | 35 (2%)               | 2.24 (1.46–3.47)  | <0.0001 |
| Paraesthesia                                      | 42 (3%)                 | 23 (2%)               | 1.90 (1.11–3.33)  | 0.013   |
| Carpal tunnel syndrome                            | 35 (2%)                 | 11 (1%)               | 3.33 (1.64–7.29)  | <0.0001 |
| Osteoporosis                                      | 97 (7%)                 | 54 (4%)               | 1.91 (1.34–2.73)  | <0.0001 |
| Muscle spasm                                      | 25 (2%)                 | 106 (7%)              | 0.23 (0.14–0.36)  | <0.0001 |
| Vasomotor or gynaecological (any)                 | 879 (61%)               | 1031 (69%)            | 0.69 (0.59–0.80)  | <0.0001 |
| Hot flushes                                       | 818 (56%)               | 899 (60%)             | 0.85 (0.73–0.99)  | 0.031   |
| Vaginal dryness                                   | 189 (13%)               | 159 (11%)             | 1.25 (1.00–1.58)  | 0.047   |
| Vaginal haemorrhage                               | 35 (2%)                 | 80 (5%)               | 0.44 (0.28–0.66)  | <0.0001 |
| Vaginal discharge                                 | 30 (2%)                 | 136 (9%)              | 0.21 (0.14–0.32)  | <0.0001 |
| Vaginal candidiasis                               | 8 (1%)                  | 42 (3%)               | 0.19 (0.08–0.41)  | <0.0001 |
| Other   |                         |                       |                   |         |
| Headache  | 82 (6%)                 | 61 (4%)               | 1.40 (0.99–2.00)  | 0.049   |
| Hypercholesterolaemia                             | 43 (3%)                 | 11 (1%)               | 4.11 (2.07–8.86)  | <0.0001 |
| Major thromboembolic                              | 7 (<1%)                 | 24 (2%)               | 0.30 (0.11–0.71)  | 0.0028  |
| Pulmonary embolism                                | 5 (<1%)                 | 8 (1%)                | 0.64 (0.16–2.23)  | 0.43    |
| Deep vein thrombosis (without pulmonary embolism) | 2 (<1%)                 | 16 (1%)               | 0.13 (0.01–0.54)  | 0.0011  |
| Any cardiovascular                                | 93 (6%)                 | 84 (6%)               | 1.15 (0.84–1.57)  | 0.38    |
| Myocardial infarction                             | 6 (<1%)                 | 6 (<1%)               | 1.03 (0.27–3.85)  | 0.99    |
| Cerebrovascular accident                          | 13 (1%)                 | 4 (<1%)               | 3.36 (1.04–14.18) | 0.025   |
| Transient ischaemic attack                        | 13 (1%)                 | 5 (<1%)               | 2.69 (0.90–9.65)  | 0.05    |
| Hypertension                                      | 82 (6%)                 | 73 (5%)               | 1.16 (0.83–1.63)  | 0.36    |
| Any eye disease                                   | 230 (16%)               | 209 (14%)             | 1.16 (0.94–1.42)  | 0.16    |
| Cataract  | 72 (5%)                 | 61 (4%)               | 1.22 (0.85–1.77)  | 0.26    |

OR=odds ratio.

**Table 4: Adverse events reported at any time according to treatment allocation**

The cutoff date for this analysis was Sept 30, 2015. Median follow-up was 7.2 years (IQR 5.6–8.9) and 21112 women-years of follow-up were accrued (10670 women-years for anastrozole and 10442 tamoxifen). 5 year adherence was estimated to be 67.6% (95% CI 65.1–70.0) in the anastrozole group compared with 67.4% (64.9–69.7) in the tamoxifen group ( $p=0.71$ ; appendix). The main reasons for treatment cessation were adverse events and patient decision (data not shown).

A total of 144 breast cancer recurrences were reported; recurrences were mostly invasive (84 [58%]; table 2). Numerically fewer recurrences occurred with anastrozole (67 recurrences; annual rate 0.64% [95% CI 0.50–0.82]) than for tamoxifen (77; 0.72% [0.58–0.90]; HR 0.89 [95% CI 0.64–1.23]; figure 2). The non-inferiority of anastrozole was established (upper 95% CI <1.25), but its superiority to tamoxifen was not ( $p=0.49$ ). Kaplan-Meier estimates of recurrence at 5 years were 2.5% (95% CI 1.8–3.5) for anastrozole and 3.0% (2.2–4.0) for tamoxifen. After 10 years of follow-up, recurrence was 6.6% (95% CI 4.9–8.8) and 7.3% (5.7–9.4), respectively.

Among the 144 recurrences, 86 (60%) were ER-positive, 30 (21%) were ER-negative, and ER status was missing for 28 (19%). Among women with ER-positive recurrences, 30 (2%) were in the anastrozole group compared with 56 (4%) in the tamoxifen group (HR 0.55 [95% CI 0.35–0.86],  $p=0.008$ ). Among women with ER-negative recurrences, 17 (1%) were in the anastrozole group compared with 13 (<1%) in the tamoxifen group (HR 1.34 [95% CI 0.65–2.75],  $p=0.43$ ).

Analyses adjusted by age, body-mass index, menopausal hormone therapy use, grade, margins, and radiotherapy subgroups yielded similar HRs as in the univariate analyses (table 2). Similar numbers of DCIS recurrences were observed in each treatment group (29 for anastrozole vs 30 for tamoxifen; HR 0.99 [95% CI 0.60–1.65],  $p=0.98$ ; table 2).

A total of 69 deaths had been reported by the cutoff date (appendix). Overall, we noted no statistically significant difference between treatment arms (33 for anastrozole vs 36 for tamoxifen; HR 0.93 [95% CI 0.58–1.50],  $p=0.78$ ) and no specific cause of death differed by treatment group. Only four deaths from breast cancer were recorded, one in the anastrozole group and three in the tamoxifen group. Overall, the frequency of cancers other than breast was not significantly different in the anastrozole and tamoxifen groups (61 vs 71; OR 0.88 [95% CI 0.61–1.26],  $p=0.47$ ; table 3). However, endometrial, ovarian, and skin cancers were significantly more common with tamoxifen (table 2).

We collected a comprehensive record of side-effects during the 5 years of treatment (table 4). The number of women reporting any event was similar between treatment groups overall (1323 for anastrozole vs 1379 for



tamoxifen) but the specific profiles were different. Fractures were significantly higher in the anastrozole group (129 vs 100; OR 1.36 [95% CI 1.03–1.80],  $p=0.027$ ) and musculoskeletal adverse events such as joint stiffness, paraesthesia, carpal tunnel syndrome, and osteoporosis were also significantly higher with anastrozole (table 4). Hypercholesterolaemia was furthermore significantly more common in women receiving anastrozole compared with those receiving tamoxifen, probably as a result of the cholesterol-reducing effects of tamoxifen. By contrast, anastrozole was associated with substantially fewer muscle spasms compared with tamoxifen (25 [2%] vs 106 [7%]; OR 0.23 [95% CI 0.14–0.36],  $p<0.0001$ ).

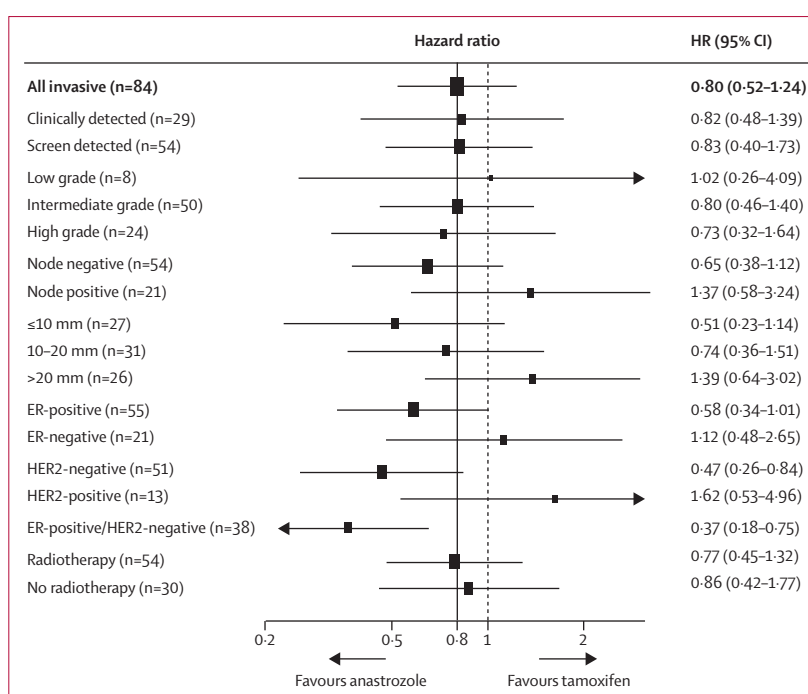
Apart from vaginal dryness, gynaecological symptoms were significantly higher with tamoxifen. Vasomotor symptoms were common in both treatment groups, but the frequency was significantly lower with anastrozole (818 [56%] vs 899 [60%]; OR 0.85 [95% CI 0.73–0.99],  $p=0.0310$ ; table 4). We noted a significant decrease in pulmonary emboli and deep vein thromboses (seven vs 24; OR 0.30 [95% CI 0.11–0.71],  $p=0.0028$ ). No statistically significant difference was seen for cardiovascular events overall or myocardial infarction in particular (table 4). However, transient ischaemic attacks (13 vs five; OR 2.69 [95% CI 0.90–9.65],  $p=0.05$ ) and particularly cerebrovascular accidents (13 vs four; 3.36 [1.04–14.18],  $p=0.025$ ) were increased with anastrozole.

Despite the differences in side-effect profiles, treatment adherence was virtually identical between treatment groups and was 67.6% for anastrozole and 67.4% for tamoxifen after 5 years (appendix).

In a post-hoc analysis, we assessed differences by subgroups of tumour for invasive recurrence (figure 3). The largest difference was noted for invasive ER-positive/HER2-negative tumours (10 recurrences with anastrozole vs 28 with tamoxifen; HR 0.37 [95% CI 0.18–0.75],  $p=0.0060$ ; figure 3). HER2-positive tumours showed better efficacy with tamoxifen (HR 1.62 [95% CI 0.53–4.96]; heterogeneity  $p=0.05$ ; figure 3).

We did not find a differential effect on recurrence according to radiotherapy use at baseline (54 recurrences with radiotherapy vs 30 with no radiotherapy; HR 0.77 [95% CI 0.49–1.21],  $p=0.25$ ). Furthermore, anastrozole was not more effective at reducing invasive recurrences in those women who had radiotherapy at baseline (HR 0.77 [95% CI 0.45–1.32],  $p=0.34$ ) compared with those who did not (0.86 [0.42–1.77],  $p=0.69$ ; heterogeneity  $p=0.79$ ; figure 3).

In a post-hoc analysis, we excluded 26 women who were found to be ineligible after randomisation (figure 1). Exclusion of these women from the primary analysis did not alter the results (data not shown). Furthermore, exclusions of the nine (<1%) women with atypical hyperplasia or lobular carcinoma in-situ from a post-hoc reassessment of the primary endpoint analysis had no effect on the results (data not shown).



**Figure 3: Subgroup analyses for invasive breast cancer by cancer characteristics**

Numbers do not add to totals because of missing values. The dotted line shows no effect point, and the bold line shows overall treatment effect point. ER=oestrogen receptor.

## Discussion

In this large, randomised, double-blind, placebo-controlled trial comparing anastrozole with tamoxifen in women with ER-positive or PgR-positive DCIS treated by wide local excision with or without breast radiotherapy, the non-inferiority of anastrozole to tamoxifen was demonstrated, but a significant superiority efficacy was not, although we noted a slightly lower recurrence rate for anastrozole. However, the overall event rate was lower than anticipated, which might have contributed to non-significant results with wide confidence intervals, and as a result smaller effects of anastrozole might have been missed. This possible small benefit for anastrozole is consistent with the larger 27% reduction seen in the similar NSABP B-35 trial, which was statistically significant ( $p=0.03$ ).<sup>10</sup> Trials in the adjuvant setting have also indicated greater efficacy for anastrozole and other aromatase inhibitors versus tamoxifen.<sup>17,18</sup> Additionally, the reduction in contralateral breast cancer is consistent with the benefits of anastrozole compared with tamoxifen seen in the ATAC trial<sup>17</sup> and compared with placebo in the IBIS-II breast cancer prevention trial.<sup>11</sup> The greater efficacy of anastrozole for ER-positive or HER2-negative invasive recurrence has been seen elsewhere for invasive disease.<sup>19</sup> HER2 status was not routinely collected for the baseline tumour, but tumour blocks are being collected retrospectively and its impact along with other markers will be reported at a later stage. Local recurrence rates were lower than those predicted on the basis of earlier trials. This is probably caused by greater attention to

achieving clear surgical margins, and improvements in and more frequent use of radiotherapy.

Clear differences were seen in the side-effect profile. Many side-effects followed the expected pattern seen during treatment of invasive cancer,<sup>18</sup> with a higher fracture rate and more musculoskeletal events with anastrozole, and more venous thromboembolic events, gynaecological events, and vasomotor symptoms with tamoxifen. The higher rate of strokes with anastrozole is surprising because this pattern was not seen in ATAC (62 strokes with anastrozole vs 80 with tamoxifen),<sup>17</sup> or the prevention component of IBIS-II (three with anastrozole vs six with placebo),<sup>11</sup> and these events were not lower for tamoxifen when compared with placebo in IBIS-I (ten with tamoxifen vs 12 with placebo).<sup>20</sup> Tamoxifen has previously been reported to reduce headache occurrence,<sup>20,21</sup> so the higher rate of headache in the anastrozole group of our trial probably resulted from this rather than the effects of anastrozole. However, increased hypertension was seen for anastrozole in both ATAC<sup>17</sup> and IBIS-II prevention;<sup>11</sup> the small increase in our anastrozole group therefore seems to be a real treatment effect, although the mechanism is not understood.

Although occurrence of other cancers was similar overall, the incidence of specific cancers differed by treatment. A two-to-three-fold increase in endometrial cancer is well documented for tamoxifen,<sup>22,23</sup> by contrast with a reduced incidence compared with the general population anticipated for anastrozole in view of the strong hormone dependence for this tumour.<sup>24</sup> In combination, these two effects account for the striking difference seen here. Ovarian cancer is not known to be affected by tamoxifen and the differences here probably result from a preventive effect of anastrozole, as previously seen in IBIS-II prevention (four cases with anastrozole vs seven with placebo) and indirectly in ATAC (ten with anastrozole vs 17 with tamoxifen), and supported by the increased risk associated with use of menopausal hormone therapy.<sup>25</sup> A decrease of colorectal cancer has been reported in users of menopausal hormone therapy;<sup>26</sup> although a small increase was reported in ATAC (39 cases with anastrozole vs 31 with tamoxifen), a lower risk was seen in IBIS-II prevention (three with anastrozole vs 11 with tamoxifen), so the role of aromatase inhibitors in affecting risk of colorectal cancer remains uncertain.

The major strengths of this study include its multinational nature, large size, moderate length of follow-up, and detailed collection of side-effect data. The major limitation of this trial was the lower-than-expected event rate, which adds uncertainty about the lack of significance of some of the small differences seen. A few unexpected side-effects were also recorded, which require further validation in view of the amount of multiple testing. It is too early to assess the effect of these treatments on mortality and long-term follow-up; a full meta-analysis of all major endpoints with the B-35 study is planned to study these issues.

In summary, anastrozole offers another option for postmenopausal women with ER-positive DCIS, and the choice between it and tamoxifen will probably depend more on previous history of other conditions (eg, osteoporosis and venous thrombosis) and short-term tolerability (musculoskeletal, vasomotor, and gynaecological symptoms) than differences in efficacy.

#### Contributors

JFF, IS, AH, GvM, and JC designed the study. JFF, IS, AH, BB, NB, CL, GvM, WE, PN, MS, CH, REC, and JC collected data. IS and JC analysed the data. JFF, IS, AH, REC, and JC wrote the report. JFF, IS, AH, BB, CL, GvM, WE, PN, MS, CH, REC, LJ, IE, and JC interpreted the data.

#### Declaration of interests

JC and GvM have received funding from AstraZeneca to conduct clinical trials. MS has received travel support from Roche. The other authors declare no competing interests.

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# THE LANCET

## **Supplementary appendix**

This appendix formed part of the original submission and has been peer reviewed.  
We post it as supplied by the authors.

Supplement to: Forbes JF, Sestak I, Howell A, et al, on behalf of the IBIS-II investigators.  
Anastrozole versus tamoxifen for the prevention of locoregional and contralateral  
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## **Appendix**

### ***Independent Trial Steering Committee***

Richard Sainsbury (University College London, United Kingdom)  
Judy Garber (Dana-Farber Cancer Institute, Boston, United States)  
Jane Warwick (The University of Warwick, Coventry, United Kingdom)

### ***Trial Participant Steering Committee***

Bernardo Bonanni (European Institute of Oncology, Milan, Italy National Coordinating Centre)  
Mary Buchanan (Patient Advocate)  
Nigel Bundred (University Hospital of South Manchester, United Kingdom)  
Katharina Buser (Swiss Group for Clinical Cancer Research, Switzerland National Coordinating Centre)  
Simon Cawthorn (Southmead Hospital, Bristol)  
Robert Coleman (Weston Park Hospital, Sheffield)  
Jack Cuzick – Co-Chairman (Queen Mary University, London)  
Mitch Dowsett (The Royal Marsden NHS Trust, London)  
Richard Eastell (Sheffield University, Sheffield)  
Bent Ejlersen (The Finsen Centre, Copenhagen, Denmark)  
Ian Ellis (University of Nottingham)  
John Forbes (Australian New Zealand Breast Cancer Trials Group, Newcastle, Australia National Coordinating Centre)  
Anthony Howell (Genesis Breast Cancer Prevention Centre, Manchester)  
Zsuzsanna Kahan (University of Szeged, Szeged, Hungary)  
Christelle Levy (Centre François Baclesse, CAEN & UNICANCER BREAST GROUP, France National Coordinating Centre)  
Robert Mansel (University of Wales College of Medicine, Cardiff)  
Patrick Neven (UZ Gasthuisberg Ziekenhuis, Leuven, Belgium National Coordinating Centre)  
Tiina Palva (Pirkanmaa Cancer Society, Tampere, Finland)  
Lisa Rydén (Skånes universitetssjukhus, Lund, Sweden National Coordinating Centre)  
Michael Stierer (Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria National Coordinating Centre)  
Mary Stuart (Astrazeneca, Macclesfield)  
Fatima Vaz (Instituto Portugues de Oncologia, Lisbon, Portugal)  
Gunter von Minckwitz (German Breast Group, Frankfurt, Germany National Coordinating Centre)

### ***Principal Investigators***

Hugo Marsiglia (Gustave Roussy, Villejuif, UCBG, France)  
Christelle Levy (C. F. Baclesse, Caen, UCBG, France)  
Ahmed Benyoucef (C. H. Becquerel, Rouen, UCBG, France)  
Dominique Berton-Rigaud (C. R. Gauducheau, Saint Herblain, UCBG, France)  
Catherine Loustalot (C. G.F. Leclerc, Dijon, UCBG, France)  
Daniel Serin (I. Sainte-Catherine, Avignon, UCBG, France)  
Pierre Kerbrat (C. E. Marquis, Rennes, UCBG, France)  
Jean-Christophe Eymard (I. J. Godinot, Reims, UCBG, France)  
Sylvia Giard-Lefevre (C. O. Lambret, Lille, UCBG, France)  
Nathalie Bonichon-Lamichhane (Clinique Tivoli, Bordeaux, UCBG, France)  
Alain Monnier (CHG, Montbéliard, UCBG, France)  
Nicole Tubiana-Mathieu (CHRU Dupuytren, Limoges, UCBG, France)  
Gilles Piot (C.M.C. Les Ormeaux, Le Havre, UCBG, France)  
Christine Tunon de Lara (Institut Bergonié, Bordeaux, UCBG, France)  
Olivier Bernard (CROMG, Agen, UCBG, France)  
Hélène Simon-Swirski (CHU A. Morvan, Brest, UCBG, France)  
Laurence Gladieff (I. Claudius Regaud, Toulouse, UCBG, France)

Marie-Joseph Fouchet-Goudier (CH Bretagne-Sud, Lorient, UCBG, France)  
 Nadine Dohollou (PolyClinique Nord Aquitaine, Bordeaux, UCBG, France)  
 Anne-Marie Elgard-Maitre (CH E. Müller, Mulhouse, UCBG, France)  
 Jean-Pierre Bergerat (CHRU, Strasbourg, UCBG, France)  
 Thierry Petit (Centre Paul Strauss, Strasbourg, UCBG, France)  
 Adina Marti (Centre Hospitalier, Auxerre, UCBG, France)  
 Caroline Toussaint (Centre Hospitalier, Lagny sur Marne, UCBG, France)  
 Francesco Del Piano (Hôpitaux du Léman, Thonon les bains, UCBG, France)  
 Mahmoud Ibrahim (CHR La Source, Orléans, UCBG, France)  
 Danièle Fric (Institut Daniel Hollard, Grenoble, UCBG, France)  
 Arnd Hönig (St. Vincenzkrankenhaus Mainz, Mainz, Germany)  
 Volkmar Müller (Universitätsklinikum Hamburg-Eppendorf, Hamburg, Germany)  
 Frederik Marmé (Universitätsklinikum Heidelberg, NCT, Heidelberg, Germany)  
 Beate Rautenberg (Uniklinik Freiburg, Freiburg, Germany)  
 Marcus Schmidt (Universitätsklinikum Mainz, Mainz, Germany)  
 Claus Hanusch (Frauenklinik vom Roten Kreuz, München, Germany)  
 Stefan Paepke (Klinikum rechts der Isar München, München, Germany)  
 Gabriele Kaltenecker (Städt. Klinikum Karlsruhe, Karlsruhe, Germany)  
 Sabine Lemster (Klinikum Schaumburg, Stadthagen, Stadthagen, Germany)  
 Joke Tio (Universitätsklinikum, Münster, Germany)  
 Toralf Reimer (Universitätsklinikum Rostock, Rostock, Germany)  
 Benjamin Schnappauf (Universitätsklinikum, Frankfurt/ Main, Germany)  
 Klaus Baumann (Universitätsklinikum, Marburg, Germany)  
 Iris Schrader (Henriettenstiftung, Hannover, Germany)  
 Christoph Mundhenke (Universitätsklinikum Schleswig-Holstein, Campus Kiel, Kiel, Germany)  
 Cornelia Liedtke (Universitätsklinikum, Lübeck, Germany)  
 Wolfgang Meinerz (St. Vincenz Krankenhaus GmbH, Paderborn, Germany)  
 Christoph Thomssen (Klinikum der Med. Fakultät, Halle/Saale, Germany)  
 Klaus Christl (Krankenhaus Eggenfelden, Eggenfelden, Germany)  
 Thomas Hitschold (Klinikum Worms gGmbH, Worms, Germany)  
 Kay Goerke (Mathias-Spital, Rheine, Germany)  
 Karin Kast (Universitätsklinikum Carl Gistav Carus an der Technischen Universität Dresden, Dresden, Germany)  
 Ingo Runnebaum (Universitätsklinikum Jena, Jena, Germany)  
 Christoph Lindner (AGAPLESION DIAKONIEKLINIKUM HAMBURG, Hamburg, Germany)  
 Peter Scheidel (Marienkrankenhaus Hamburg, Hamburg, Germany)  
 Uwe Herwig (Albertinen-Krankenhaus, Hamburg, Germany)  
 Nikola Bangemann (Charité Mitte-Campus Benjamin Franklin, Berlin, Germany)  
 Harald Sommer (I. Universitäts-Frauenklinik, München, Germany)  
 Kornelia Göhring (Klinikum Aschaffenburg, Aschaffenburg, Germany)  
 Augustinus Tulusan (Klinikum Bayreuth, Bayreuth, Germany)  
 Eva Stauß (Universitätsklinikum, Tübingen, Germany)  
 Günter Köhler (Universitätsmedizin Greifswald, Greifswald, Germany)  
 Dirk Zahm (Brustzentrum Ostthüringen am SRH Wald-Klinikum Gera, Gera, Germany)  
 Doris Augustin (Klinikum Deggendorf, Deggendorf, Germany)  
 Andrea Hocke (Universitätsfrauenklinik Bonn, Bonn, Germany)  
 Tanja Neunhöffer (Dr.-Horst-Schmidt-Kliniken GmbH, Wiesbaden, Germany)  
 Sabine Schmatloch (Elisabeth Krankenhaus GmbH, Kassel, Germany)  
 Georg Heinrich (Praxis Dr. Heinrich, Fürstenwalde, Germany)  
 Sabine Groß (Marienhospital, Stuttgart, Germany)  
 G.P. Breitbach (Marienhausklinik St. Josef-Kohlhof, Neunkirchen, Germany)  
 Anton Scharl (Klinikum St. Marien Amberg, Amberg, Germany)  
 Peter Klare (Praxisklinik Krebsheilkunde für Frauen, Berlin, Germany)  
 Andrea Stefek (Johanniter-Krankenhaus der Altmark, Stendal, Germany)  
 Gerald Hoffmann (St. Josefs hospital, Wiesbaden, Germany)

Franca Martignoni (Uniklinikum Duesseldorf, Duesseldorf, Germany)  
 Erich Weiss (Klinikum Sindelfingen-Böblingen gGmbH, Böblingen, Germany)  
 Günter Emons (Universitätsklinikum, Göttingen, Germany)  
 Hans-Christian Tesch (Onkologie Bethanien / Marien-KHS, Frankfurt, Germany)  
 Matthias Beckmann (Friedrich-Alexander-Universität, Erlangen, Germany)  
 Rita Schmutzler (Universitätsklinikum Köln, Koeln, Germany)  
 Martin Schütte (Katholische Kliniken Essen-Nord, Essen, Germany)  
 Bahriye Aktas (Universitätsklinikum, Essen, Germany)  
 Ursula Hille-Betz (Medizinische Hochschule, Hannover, Germany)  
 Mustafa Deryal (Caritasklinik St. Theresia, Saarbrücken, Germany)  
 Serban Dan Costa (Otto-v.-Guericke-Universität, Magdeburg, Germany)  
 Beate Blümel (Onkologische Schwerpunktpraxis, Magdeburg, Germany)  
 Uwe-Jochen Göhring (Johanniter-Krankenhaus, Bonn, Germany)  
 Anke Kleine-Tebbe (DRK-Kliniken Berlin Köpenick, Berlin, Germany)  
 Claudia Schumacher (St.Elisabeth-KKH, Koeln, Germany)  
 Jasmin/Christoph Pourfard/Uleer (Gemeinschaftspraxis Hildesheim, Hildesheim, Germany)  
 Uwe Kullmer (Asklepios Paulinen Klinik, Wiesbaden, Germany)  
 Petra Krabisch (Klinikum Chemnitz, Chemnitz, Germany)  
 Regine Gätje (Alfried-Krupp Krankenhaus, Essen, Germany)  
 Thomas Schwenzer (Klinikum Dortmund, Dortmund, Germany)  
 Hans-Joachim Hindenburg (Praxis Dr. Hindenburg, Berlin, Germany)  
 Andreas Rempen (Diakonie-Klinikum Schwäbisch HallgGmbH, Schwäbisch Hall, Germany)  
 Heinz-Gert Höffkes (Klinikum Fulda, Fulda, Germany)  
 Elmar Stickeler (Brustzentrum Südbaden, Freiburg, Germany)  
 Christian Reffert (Westpfalz-Klinikum GmbH, Kaiserslautern, Germany)  
 Stephan Seitz (Caritas-Krankenhaus St. Josef, Regensburg, Germany)  
 Gerd Splitt (Facharzt f. Frauenheilkunde u. Geburtshilfe, Güstrow, Germany)  
 Petra Böhne (Pius-Hospital Oldenburg, Oldenburg, Germany)  
 Karsten Gnauert (Ostalbkrankenhaus, Aalen, Germany)  
 Hans-Joachim Strittmatter (Kreiskrankenhaus Schorndorf, Schorndorf, Germany)  
 Gerold Baake (Onkologische Gemeinschaftspraxis, Pinneberg, Germany)  
 Mahdi Rezai (Luisenkrankenhaus Duesseldorf, Duesseldorf, Germany)  
 Thomas Noesselt (Sana Klinikum Hameln-Pyrmont, Hameln, Germany)  
 C.-H. Köhne (Klinikum Oldenburg, Oldenburg, Germany)  
 Volker Hanf (Klinikum Fürth, Fürth, Germany)  
 Dirk Strumberg (Marienhospital, Herne, Germany)  
 Peter Dall (Klinikum Lüneburg, Lüneburg, Germany)  
 Peter/Bernd Schleicher (Gemeinschaftspraxis Dr. Bern Schleicher/ Peter Schleicher, Schwandorf, Germany)  
 Frank Beldermann (Karl Olga KKH, Stuttgart, Germany)  
 Michael Berghorn (Allgemeines Krankenhaus Celle, Celle, Germany)  
 Dirk-Thoralf Baerens (Frauenarztpraxis, Ilsede, Germany)  
 Hans-Christian Kolberg (Marienhospital, Bottrop, Germany)  
 Lelia Bauer (Krankenhaus Weinheim, Weinheim, Germany)  
 Cosima Brucker (Klinikum Nürnberg, Nürnberg, Germany)  
 Iris Schrader (Gynäkologisch, onkologische Gemeinschaftspraxis, Hannover, Germany)  
 Thomas Steck (Klinikum Passau, Passau, Germany)  
 Frances Boyle (Mater Hospital, North Sydney, Australia)  
 John Forbes (Calvary Mater Newcastle, Waratah, Australia)  
 Anupam Chaudhuri (Riverina Cancer Care Centre, Wagga Wagga, Australia)  
 Eugene Moylan (Liverpool Hospital, Liverpool, Australia)  
 Jenny Donovan (Royal North Shore Hospital, St. Leonards, Australia)  
 Stephen Della-Fiorentina (Southern Highlands Cancer Centre, Bowral, Australia)  
 Ehtesham Abdi (The Tweed Hospital, Tweed Heads, Australia)  
 Gavin Marx (San Clinical Trials Unit, Wahroonga, Australia)

Geoffrey Beadle (Royal Brisbane & Women's Hospital, Herston, Australia)  
 Michael Donovan (Nambour Hospital, Nambour, Australia)  
 Ian Bennett (Princess Alexandra Hospital, Woolloongabba, Australia)  
 Peter Grantley Gill (Royal Adelaide Hospital, Adelaide, Australia)  
 Caroline Baker (Austin Heath, Heidelberg, Australia)  
 Richard Masters (Box Hill Hospital, Box Hill, Australia)  
 Robert Blum (The Bendigo Hospital, Bendigo, Australia)  
 John Collins (Royal Melbourne Hospital, Parkville, Australia)  
 Michael Law (Maroondah Hospital, Ringwood East, Australia)  
 Stewart Hart (Monash Medical Centre, East Bentleigh, Australia)  
 Caroline Baker (Victorian Breast & Oncology Care, East Melbourne, Australia)  
 George Kannourakis (Ballarat Oncology & Haematology Services, Wendouree, Australia)  
 Raymond Snyder (St Vincent's Hospital, Fitzroy, Australia)  
 David Joseph (Sir Charles Gairdner Hospital, Nedlands, Australia)  
 Michael McCrystal (North Shore Hospital (Waitemata), Auckland, New Zealand)  
 Ian Campbell (Waikato Hospital, Hamilton, New Zealand)  
 Raimund Jakesz (Vienna University Medical School, Vienna, Austria)  
 Ursula Selim (Brustzentrum Hanusch-KH, Vienna, Austria)  
 Christian Singer (Medical University of Vienna, Vienna, Austria)  
 Dietmar Heck (KH BHS Linz, Linz, Austria)  
 Richard Greil (St. Johanns Hospital, Salzburg, Austria)  
 Angela Ramoni (Innsbruck Univ. Medical School, Innsbruck, Austria)  
 Vesna Bjelic-Radisic (Graz Univ. Med. School, Graz, Austria)  
 Arno Reichenauer (BHB Hospital Sankt Veit, Sankt Veit, Austria)  
 Wilfried Horvath (Gussing Hospital, Gussing, Austria)  
 Josef Thaler (Hospital Klinikum Kreuzschwestern Wels, Oberösterreich, Austria)  
 Michael Fridrik (General Hospital Linz, Linz, Austria)  
 Joerg Keckstein (LKH Villach, Villach, Austria)  
 Lamote Jan (AZ-VUB, Borstkliniek, Brussels, Belgium)  
 Marc L'Hermitte (CHU-UCV Brugmann, Brussels, Belgium)  
 Heidi Roelstrate (OLVrouwziekenhuis Aalst, Aalst, Belgium)  
 Luc Dirix (AZ St. Augustinus, Wilrijk, Belgium)  
 Inneke Bambust (AZ St. Blasius, Dienst Oncologie, Dendermonde, Belgium)  
 Monique Seret (St. Elisabeth ZH, Namur, Belgium)  
 Fabienne Liebens (CHU St. Pierre, Brussels, Belgium)  
 Maria Maerevoet (Clinique St. Pierre, Ottignies, Belgium)  
 Lionel D'Hondt (CHU Dinant Godinne, Yvoir, Belgium)  
 Martine Berliere (Université Catholique de Louvain, Brussels, Belgium)  
 Jean-Marie Nogaret (Institut Jules Bordet, Brussels, Belgium)  
 Phillipe Simon (Erasmus ZH, Brussels, Belgium)  
 Tiina Palva (Pirkanmaa Cancer Society, Tampere, Finland)  
 Zsuzsanna Kahan (Department of Oncotherapy, University of Szeged, Szeged, Hungary)  
 Deirdre O'Hanlon (Dept of Surgery, Cork, Ireland)  
 Henry Paul Redmond (Department of surgery, Cork, Ireland)  
 Arnold Hill (Surgical Professorial Unit, Beaumont Dublin, Ireland)  
 Denis Evoy (Department of Surgery, UC Dublin, Ireland)  
 Michael Kerin (University College Hospital, Galway, Ireland)  
 Rajnish Gupta (Midwestern Cancer Centre, Limerick, Ireland)  
 Michael J. Martin (Sligo General Hospital, Sligo, Ireland)  
 Marcela Fritis (Fundacion Arturo Lopez Perez, Santiago, Chile)  
 Ricardo Schwartz (Hospital Militar, Santiago, Chile)  
 Maria Loreto Yañez (Instituto de Radiomedicina, Santiago, Chile)  
 Octavio Peralta (Hospital Clinico San Borja Arriarán, Santiago, Chile)  
 Claudio Graiff (Azienda Sanitaria di Bolzano, Bolzano, Italy)  
 Fabrizio Artioli (Ospedale B. Ramazzini, V. Guido Molinari, Modena, Italy)



Daniele Generali (Azienda Istituti Ospitalieri di Cremona, Cremona, Italy)  
 Lorenzo Orzalesi (Universita degli studi Firenze, Florence, Italy)  
 Marilena Visini (Azienda Ospedaliera Ospedale di Lecco, Lecco, Italy)  
 Bernardo Bonanni (Istituto Europeo di Oncologia, Milan, Italy)  
 Maria Michiara (Azienda Ospedaliero-Universitaria di Parma, Parma, Italy)  
 Lorenzo Pavesi (Fondazione Salvatore Maugeri, Pavia, Italy)  
 Alberto Ravaioli (Azienda Unita Sanitaria Locale di Rimini, Rimini, Italy)  
 Mauro Porpiglia (Aso O.I.R.M. Sant'anna, Turin, Italy)  
 Fabio Puglisi (Policlinico Universitario di Udine, Udine, Italy)  
 Graziella Pinotti (Ospedale di Circolo, Varese, Italy)  
 Stephen Brincat (Sir Anthony Mamo Oncology Centre, Tal Qroqq, Malta)  
 Katharina S. Buser (Oncocare Klinik Engeried, Bern, Switzerland)  
 Manuela Rabaglio (Klinik und Poliklinik fuer Medizinische Onkologie, Inselspital, Bern, Switzerland)  
 Daniel Rauch (SpitalSTS AG Simmenthal-Thun-Saanenland, Thun, Switzerland)  
 Pierre O. Chappuis (HUG Unite d'oncogénétique et de prévention, Service d'Oncologie, Genève, Switzerland)  
 Khalil Zaman (Centre pluridisciplinaire d'oncologie, CHUV, Lausanne, Switzerland)  
 Susanne Bucher (Neue Frauenklinik, Luzern, Switzerland)  
 Barbara Bolliger (Center for Tumordetection and Prevention (ZETUP), St. Gallen, Switzerland)  
 Olivia Pagani (Institute of Oncology of Southern Switzerland, Bellinzona, Switzerland)  
 Anna-Karin Falck (Helsingborg Lasarett Helsingborg, Sweden)  
 Lisa Rydén (Skånes Universitetssjukhus, Lund, Sweden)  
 Jakob Kaij (Skånes Universitetssjukhu, Malmo, Sweden)  
 Sara Margolin (Karolinska University Hospital at Södersjukhuset, Stockholm, Sweden)  
 Mahmut Muslumanoglu (Istanbul University, Istanbul, Turkey)  
 Gianfilippo Bertelli (Singleton Hospital, Swansea, United Kingdom)  
 Maria Bramley (The Royal Oldham Hospital, United Kingdom)  
 James Bristol (Cheltenham General Hospital, United Kingdom)  
 Sankaran Chandrasekharan (Essex County Hospital, Colchester, United Kingdom)  
 Perrie Crellin (Dorchester County Hospital, United Kingdom)  
 Raouf Daoud (Frimley Park Hospital NHS Trust, United Kingdom)  
 David Dodwell (York Hospital, United Kingdom)  
 Philip Drew (Royal Cornwall Hospital, Truro, United Kingdom)  
 Sidharth Dubey (Derriford Hospital, Devon, United Kingdom)  
 Abigail Evans (Poole Hospital NHS Foundation Trust, United Kingdom)  
 Douglas Ferguson (Royal Devon and Exeter Hospital, United Kingdom)  
 Raafat Gendy (Mid Staffordshire NHS Foundation Trust, United Kingdom)  
 Hisham Hamed (Guys Hospital, London, United Kingdom)  
 Claudia Harding-McKean (Countess of Chester Hospital, United Kingdom)  
 Chris Holcombe (Royal Liverpool University Hospital, United Kingdom)  
 Kieran Horgan (St James' Hospital, Leeds, United Kingdom)  
 Shabana Iqbal (Huddersfield Royal Infirmary, United Kingdom)  
 Jibril A. Jibril (United Lincolnshire Hospitals NHS Trust, United Kingdom)  
 Jalal Kokan (Macclesfield District General Hospital, United Kingdom)  
 Peter Kneeshaw (The Hull and East Yorkshire Breast Care Unit, United Kingdom)  
 Mark Lansdown (St James' Hospital, Leeds, United Kingdom)  
 Tom Lennard (University of Newcastle upon Tyne, United Kingdom)  
 Rick Linforth (St Lukes Hospital, Bradford, United Kingdom)  
 Robert Mansel (University of Wales College of Medicine, Cardiff, United Kingdom)  
 Stuart McIntosh (Belfast City Hospital, United Kingdom)  
 Sankha Mitra (Worthing and Southlands Hospital, United Kingdom)  
 Glyn Neades (Western General Hospital, Edinburgh, United Kingdom)  
 Jane Louise Ooi (Royal Bolton Hospital, United Kingdom)  
 Ashraf Patel (St. Margaret's Hospital, Epping, United Kingdom)  
 Zenon Rayter (Bristol Royal Infirmary, United Kingdom)

Robert Reichert (Northwick Park Hospital, Harrow, United Kingdom)  
 Fiona Roberts (St. James's University Hospital, Wakefield, United Kingdom)  
 Nicola Roche (Royal Marsden Hospital, London, United Kingdom)  
 Colin Rogers (Queens Hospital Burton, Burton-on-Trent, United Kingdom)  
 Gavin Royle (Princess Anne Hospital, Southampton, United Kingdom)  
 Elizabeth Shah (East Sussex Hospitals NHS Trust, United Kingdom)  
 Mark Sibbering (Royal Derby Hospital, United Kingdom)  
 Anthony Iain Skene (Royal Bournemouth Hospital, United Kingdom)  
 Simon Smith (Broomfield Hospital, Chelmsford, United Kingdom)  
 Geoffrey Sparrow (Yeovil District Hospital, Yeovil, United Kingdom)  
 Alastair Thompson (Ninewells Hospital, Dundee, United Kingdom)  
 Jayant Vaidya (Royal Free and UCL Medical School, London, United Kingdom)  
 Virginia Wolstenholme (St Bartholomew's Hospital, London, United Kingdom)  
 Jeremy Wood (Queen Elizabeth II Hospital, Welwyn Garden City, United Kingdom)  
 Constantinos Yiangou (Queen Alexandra Hospital, Portsmouth, United Kingdom)  
 Charles Zammit (Royal Sussex County Hospital, Brighton, United Kingdom)

### ***Local Coordinating Centres***

Rochelle Thornton (Australian New Zealand Breast Cancer Trials group, Newcastle, Australia)  
 Flonda Probert (Australian New Zealand Breast Cancer Trials group, Newcastle, Australia)  
 Akiko Fong (Australian New Zealand Breast Cancer Trials group, Newcastle, Australia)  
 Nicole Francis (Australian New Zealand Breast Cancer Trials group, Newcastle, Australia)  
 Manuela Gili (Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria)  
 Rosita Eigenberger (Austrian Breast and Colorectal Cancer Study Group, Vienna, Austria)  
 Daisy Supply (University Hospitals, Leuven, Belgium)  
 Inge Lefever (University Hospitals, Leuven, Belgium)  
 Bettina Muller (Chilean Cooperative Group for Oncologic Research (GOCCHI), Santiago, Chile)  
 Zdenka Zlatař (Chilean Cooperative Group for Oncologic Research (GOCCHI), Santiago, Chile)  
 Petra Feer (GBG Forschungs GMBH, Frankfurt, Germany)  
 Ioannis Gkantiragas (GBG Forschungs GMBH, Frankfurt, Germany)  
 Marjo Virkki (Tampere, Tampere, Finland)  
 Sibille Everhard (La Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France)  
 Jerome Lemonnier (La Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France)  
 Sara Garcia (La Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France)  
 Saliha Ghanem (La Fédération Nationale des Centres de Lutte Contre le Cancer, Paris, France)  
 Anna Cole (All Ireland Cooperative Clinical Research Group (ICORG), Cork, Ireland)  
 Debra O'Hare (All Ireland Cooperative Clinical Research Group (ICORG), Cork, Ireland)  
 Elaine Cronin (All Ireland Cooperative Clinical Research Group (ICORG), Cork, Ireland)  
 Trudi Roche (All Ireland Cooperative Clinical Research Group (ICORG), Dublin, Ireland)  
 Emer Kennedy (All Ireland Cooperative Clinical Research Group (ICORG), Dublin, Ireland)  
 Jo Ballot (All Ireland Cooperative Clinical Research Group (ICORG), Dublin, Ireland)  
 Niamh Killilea (All Ireland Cooperative Clinical Research Group (ICORG), Galway, Ireland)  
 Marian Jennings (All Ireland Cooperative Clinical Research Group (ICORG), Galway, Ireland)  
 Laura Lowry (All Ireland Cooperative Clinical Research Group (ICORG), Limerick, Ireland)  
 Moira Maxwell (All Ireland Cooperative Clinical Research Group (ICORG), Sligo, Ireland)  
 Margaret Burke (All Ireland Cooperative Clinical Research Group (ICORG), Sligo, Ireland)  
 Aliana Guerrieri Gonzaga (Istituto Europeo di Oncologia, Milan, Italy)  
 Giorgia Bollani (Istituto Europeo di Oncologia, Milan, Italy)  
 Andrea Bianchetti (A.O. Papa Giovanni XXIII, Bergamo, Italy)  
 Anna Scalvini (A.O. Spedali Civili di Brescia, Brescia, Italy)  
 Elisabetta Cretella (Azienda Sanitaria di Bolzano, Bolzano, Italy)  
 Antonella Pasqualini (Ospedale B. Ramazzini, Carpi, Italy)  
 Angela Gobbi (Az. Istituti Ospitalieri di Cremona, Cremona, Italy)  
 Jenny Roselli (Policlinico Careggi Università di Firenze, Florence, Italy)

Angelita Lagati (Azienda Ospedaliera Ospedale di Lecco, Lecco, Italy)  
 Elena Rapacchi (Azienda Ospedaliero-Universitaria di Parma, Parma, Italy)  
 Annalisa Lanza (Fondazione Salvatore Maugeri, Pavia, Italy)  
 Emanuela Pini (Azienda USL della Romagna Ospedale Infermi Rimini, Rimini, Italy)  
 Elisa Picardo (Azienda Ospedaleiera Sant'Anna, Turin, Italy)  
 Furio Maggiorotto (Istituto per la Ricerca e Cura del Cancro, Candiolo (TO), Italy)  
 Roberta Sottile (Policlinico Universitario di Udine, Udine, Italy)  
 Ilaria Vallini (Ospedale di Circolo e Fondazione Macchi, Varese, Italy)  
 Nadia Cilia (Sir Anthony Mamo Oncology Centre, Tal Qroqq, Malta)  
 Mital Patel (Barts Hospital, London, United Kingdom)  
 Linda Bamford (Bradford Royal Infirmary, Bradford, United Kingdom)  
 Helen Robertshaw (Bradford Royal Infirmary, Bradford, United Kingdom)  
 Hayle Inman (Bradford Royal Infirmary, Bradford, United Kingdom)  
 Naomi Hill (Belfast City Hospital, Belfast, United Kingdom)  
 Jane Dexter (Royal Sussex County Hospital Brighton, United Kingdom)  
 Emily Peasgood (Royal Sussex County Hospital, Brighton, United Kingdom)  
 Imogen Batty (Royal Bournemouth Hospital, Bournemouth, United Kingdom)  
 Shirley Cocks (Royal Bolton Hospital, Bolton, United Kingdom)  
 Raksha Mistry (Royal Bolton Hospital, Bolton, United Kingdom)  
 Mary Sidders (Bristol Royal Infirmary, Bristol, United Kingdom)  
 Emily Foulstone (Bristol Royal Infirmary, Bristol, United Kingdom)  
 Helen Garlicka (Southmead Hospital, Bristol, United Kingdom)  
 Catherine Dawe (Southmead Hospital, Bristol, United Kingdom)  
 Jackie Elliott (Queens Hospital Burton, Burton-on-Trent, United Kingdom)  
 Kathy Rooke (Essex County Hospital, Colchester, United Kingdom)  
 Christine Morris (University Hospital of Llandough, Cardiff, United Kingdom)  
 Yvonne Lester (Mid Essex Hospital Services NHS Trust, Chelmsford, United Kingdom)  
 Sian Gibson (Mid Essex Hospital Services NHS Trust, Chelmsford, United Kingdom)  
 Jill Chittock (Cheltenham General Hospital, Cheltenham, United Kingdom)  
 Amy Skelton (Cheltenham General Hospital, Cheltenham, United Kingdom)  
 Elizabeth Gallimore (Countess of Chester Hospital, Chester, United Kingdom)  
 Charlotte Downes (Royal Derby Hospital, Derby, United Kingdom)  
 Lynn Billett (Dorchester County Hospital, Dorchester, United Kingdom)  
 Simone Caddy (Dorchester County Hospital, Dorchester, United Kingdom)  
 Helen Cumming (Ninewells Hospital, Dundee, United Kingdom)  
 Sharon Cowell-Smith (Western General, Edinburgh, United Kingdom)  
 Caroline Turner (Princess Alexandra Hospital, Epping, United Kingdom)  
 Sunjalee Fernando (Princess Alexandra Hospital, Epping, United Kingdom)  
 Sarah Goodwin (Conquest Hospital, St Leonards On Sea, United Kingdom)  
 Jo-Anne Taylor (Conquest Hospital, St Leonards On Sea, United Kingdom)  
 Kizzy Baines (Royal Devon and Exeter Hospital, Exeter, United Kingdom)  
 Susan Downer (Royal Devon and Exeter Hospital, Exeter, United Kingdom)  
 Alice Pilcher (Frimley Park Hospital, Frimley, United Kingdom)  
 Tracey Dobson (Queen Alexandra Hospital, Portsmouth, United Kingdom)  
 Lynn Osborne (Grantham and District Hospital, Grantham, United Kingdom)  
 Greg Kuenzig (Guy's & St Thomas' NHS Foundation Trust, London, United Kingdom)  
 Denise Hancock (Huddersfield Royal Infirmary, Huddersfield, United Kingdom)  
 Deborah Melia (Huddersfield Royal Infirmary, Huddersfield, United Kingdom)  
 Clinical Trials Department Pharmacy (Castle Hill Hospital, Cottingham, United Kingdom)  
 Elaine Gullaksen (Castle Hill Hospital, Cottingham, United Kingdom)  
 Susan Hartup (St James's University Hospital, Leeds, United Kingdom)  
 Amy Henson (St James's University Hospital, Leeds, United Kingdom)  
 Jane Gibb (St James's University Hospital, Leeds, United Kingdom)  
 Sarah Coombs (Lincoln County Hospital, Lincoln, United Kingdom)  
 Caroline Taylor (Lincoln County Hospital, Lincoln, United Kingdom)

Amy Kirkby (Pilgrim Hospital, Lincoln, United Kingdom)  
Issy Thomas (Pilgrim Hospital, Lincoln, United Kingdom)  
Karen Makinson (Royal Liverpool University Hospital, Liverpool, United Kingdom)  
Yukie Kano (Royal Marsden Hospital, London, United Kingdom)  
Zoheb Shah (Royal Marsden Hospital, London, United Kingdom)  
Lisa Hardstaff (Macclesfield Hospital, Macclesfield, United Kingdom)  
Barbara Townley (Macclesfield Hospital, Macclesfield, United Kingdom)  
Philippa Hill (Macclesfield Hospital, Macclesfield, United Kingdom)  
Marilyn McCurrie (Macclesfield Hospital, Macclesfield, United Kingdom)  
Sue Grassby (University Hospital of South Manchester, Manchester, United Kingdom)  
Pamela Henderson (Royal Victoria Infirmary, Newcastle-Upon-Tyne, United Kingdom)  
Elizabeth Talbot (Royal Victoria Infirmary, Newcastle-Upon-Tyne, United Kingdom)  
Ashley Bell (Royal Victoria Infirmary, Newcastle-Upon-Tyne, United Kingdom)  
Reshma Kanani (Northwick Park Hospital, Northwick Park, United Kingdom)  
Joanne Johnson (Royal Oldham Hospital, Oldham, United Kingdom)  
Richard Jones (Royal Oldham Hospital, Oldham, United Kingdom)  
Mel Foster (Poole Hospital, Poole, United Kingdom)  
Becky Troke (Poole Hospital, Poole, United Kingdom)  
Hilary Congdon (Derriford Hospital, Plymouth, United Kingdom)  
Julie Pascoe (Derriford Hospital, Plymouth, United Kingdom)  
Sian Whelan (Singleton Hospital, Swansea, United Kingdom)  
Jenna Edwards (Singleton Hospital, Swansea, United Kingdom)  
Elaine Brinkworth (Singleton Hospital, Swansea, United Kingdom)  
Sheila Blizard (Weston Park Hospital, Sheffield, United Kingdom)  
Alison Clarke (Weston Park Hospital, Sheffield, United Kingdom)  
Kim Stevens (Southampton General Hospital, Southampton, United Kingdom)  
Carol Harvey (Staffordshire General Hospital, Stafford, United Kingdom)  
Jill Stacey (Staffordshire General Hospital, Stafford, United Kingdom)  
Sadie Mitchell (Royal Cornwall Hospital, Truro, United Kingdom)  
Tracey Lowry (Pinderfields Hospital, Wakefield, United Kingdom)  
Sarah Buckley (Pinderfields Hospital, Wakefield, United Kingdom)  
Clare Collins (Queen Elizabeth II Hospital, Welwyn Garden, United Kingdom)  
Liz Green (Queen Elizabeth II Hospital, Welwyn Garden, United Kingdom)  
Helen Jones (Worthing and Southlands Hospital, Worthing, United Kingdom)  
Veronica Conteh (Whittington Hospital, Whittington, United Kingdom)  
Tracey Duckett (Yeovil District Hospital, Yeovil, United Kingdom)  
Michelle Kotze (Yeovil District Hospital, Yeovil, United Kingdom)  
Paula Strider (York Hospital, York, United Kingdom)  
Marina Stouraitis (SAKK - Swiss Group for Clinical Cancer Research, Bern, Switzerland)  
Jan Sundberg (Lund University Hospital, Lund, Sweden)

***Independent Data Monitoring Committee***

Abdel Babiker (Medical Research Council Clinical Trials Unit, University College London)  
Rory Collins (University of Oxford)  
Jan Klijn (Erasmus Medical Centre, Rotterdam, Netherlands)  
Stuart Ralston (University of Edinburgh)  
Martin Tattersall (University of Sydney, Australia)  
Ian Weller (University College London)

***IBIS-II Coordinating Centre, Queen Mary University of London***

Andreia De Sousa  
Rob Edwards  
Sheila Ferguson  
Jane Hickman  
Damian Johnson

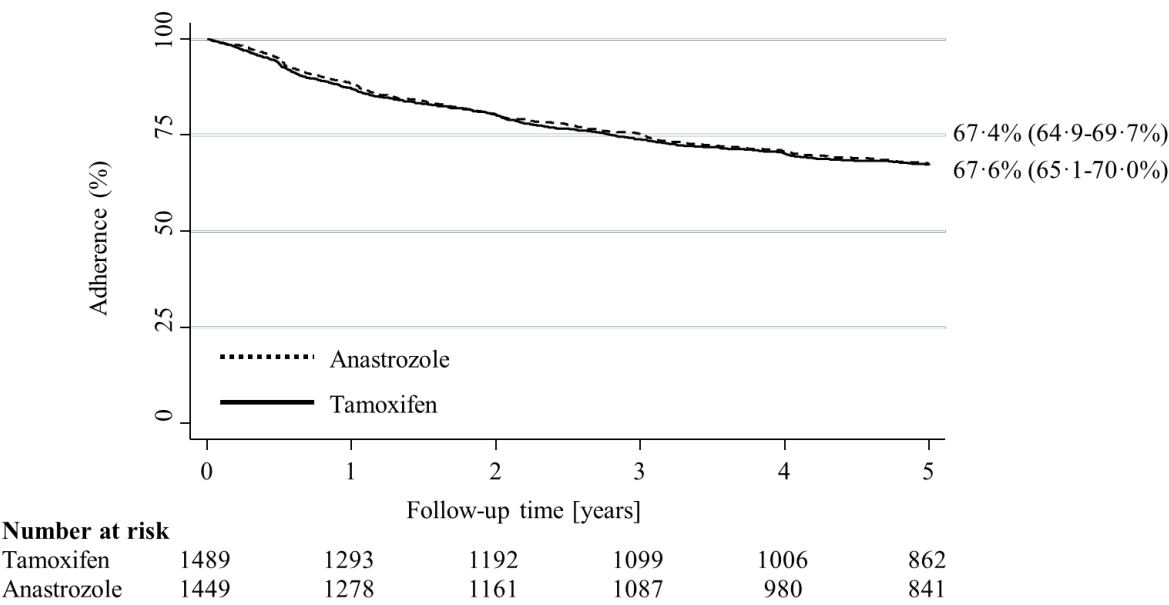
Nadia Haidar  
Victoria Hammond  
Emma Heighway  
Amalia Ndoutoumou  
Navdip Sahota  
Laura White

***Cancer Research UK Barts Clinical Trials Unit, Cancer Prevention Trials Unit***

Benoit Aigret  
Priyanka Batra  
Jill Knox  
Adedayo Oke  
Richard Ostler  
Peter Sasieni



**Supplementary Figure 1:** Five year adherence according to treatment allocation.



**Supplementary Table 1:** Cause of death by treatment allocation.

|                           | <b>Anastrozole<br/>(N=1449)</b> | <b>Tamoxifen<br/>(N=1489)</b> |
|---------------------------|---------------------------------|-------------------------------|
| <b>All</b>                | <b>33 (2·3%)</b>                | <b>36 (2·4%)</b>              |
| Breast cancer             | 1                               | 3                             |
| Other cancer              | 15                              | 12                            |
| Colorectal cancer         | 2                               | 2                             |
| Lung cancer               | 6                               | 2                             |
| Endometrial cancer        | 0                               | 1                             |
| Pancreas cancer           | 1                               | 3                             |
| CVA/Stroke/Thromboembolic | 5                               | 7                             |
| Myocardial infarction     | 2                               | 2                             |
| Other                     | 4                               | 5                             |
| Unknown                   | 6                               | 7                             |

\*CVA=Cerebrovascular accident