The ATAC (‘Arimidex’, Tamoxifen, Alone or in Combination) adjuvant breast cancer trial: first results of the endometrial sub-protocol following 2 years of treatment

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BACKGROUND: Tamoxifen treatment results in a doubling of the risk of endometrial cancer after 1–2 years of treatment and a quadrupling after 5 years. Anastrozole, a third-generation aromatase inhibitor, with superior efficacy to tamoxifen, may also offer tolerability benefits in terms of effects on the endometrium.

METHODS AND RESULTS: A sub-protocol of the ATAC trial compared the incidence/type of intrauterine changes following treatment with these agents in a subgroup of patients (n = 285) from the main trial. After 2 years anastrozole treatment, endometrial thickness remained ≤ 5 mm (baseline: 3.0 mm); in patients receiving tamoxifen, endometrial thickness increased by 3.2 mm to 7.0 mm, with a similar trend in the combination group. At baseline, 26/285 patients (9.1%) had endometrial abnormalities, most commonly polyps. After 2 years the number of endometrial abnormalities appeared lower with anastrozole treatment compared with tamoxifen although these differences were not statistically significant (odds ratio: 0.44; 95% confidence interval 0.146, 1.314; P = 0.14). Most abnormalities occurred within the first year of treatment (anastrozole: 4/6; tamoxifen: 7/10; combination: 10/16; total: 21/32). Fewer patients in the anastrozole group (1.4%) required medical intervention (tamoxifen 12.5%; combination 13.6%). CONCLUSIONS: Fewer endometrial abnormalities occurred during 2 years treatment with anastrozole compared with tamoxifen although statistical significance was not reached in this sub-protocol analysis.

Key words: anastrozole/ATAC/breast cancer/endometrial pathology/tamoxifen

Introduction

Tamoxifen has been the ‘gold standard’ for the endocrine treatment of breast cancer for the past 30 years. Its partial oestrogen agonist activity can, however, result in unwanted effects on other estrogen-sensitive target tissues, in particular the endometrium. An increase in the risk of developing endometrial cancer associated with tamoxifen treatment was first reported by Fornander et al. (1989). Since this time, tamoxifen has been shown to double the risk of endometrial cancer after 1 or 2 years of treatment, and to quadruple the risk after 5 years of treatment (Early Breast Cancer Trialists’ Collaborative Group, 1998). The relationship between tamoxifen and endometrial cancer is time-dependent and irrespective of dose, and the risk does not decrease after cessation of treatment (Bergman et al., 2000).

In May 2002, the prescribing information for tamoxifen was updated to include long-term follow-up data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 prevention study (median follow-up 6.9 years). In this study, in addition to increased risk of endometrial carcinoma, tamoxifen use was also associated with an increase in the risk of developing the more rare and more aggressive uterine sarcoma (incidence rate per 1000 women-years 0.17 with tamoxifen versus 0.0 with no tamoxifen) (Wickerham et al., 2002). Until recently, however, with no alternative endocrine treatment option available for early breast cancer (EBC), the benefits of adjuvant tamoxifen were considered to outweigh the risks (Early Breast Cancer Trialists’ Collaborative Group, 1998).

Anastrozole (‘Arimidex’) is a potent, highly selective, third-generation aromatase inhibitor that has already demonstrated superior efficacy and tolerability compared with tamoxifen in the treatment of hormone receptor-positive advanced breast cancer (ABC) in post-menopausal women (Bonnetterre et al., 2000; Nabholz et al., 2000), and has now shown long-term...
efficacy and tolerability benefits over tamoxifen for the treatment of EBC in the ‘Arimidex’, Tamoxifen, Alone or in Combination (ATAC) trial (ISRCTN 18233230) (ATAC Trialists’ Group, 2005). The ATAC trial is a randomized, double-blind study comparing anastrozole, alone or in combination with tamoxifen, relative to tamoxifen alone as a 5 year adjuvant treatment for post-menopausal women with EBC. The completed treatment analysis of the ATAC trial, at a median follow-up of 68 months, has shown that anastrozole significantly prolongs disease-free survival [DFS; hazard ratio: 0.87; 95% confidence interval (CI): 0.78, 0.97; \( P = 0.01 \)], and time-to-recurrence (TTR; hazard ratio: 0.79; 95% CI: 0.70, 0.90; \( P = 0.0005 \)) and significantly reduced distant metastases (hazard ratio: 0.86; 95% CI: 0.74, 0.99; \( P = 0.04 \)) and contralateral breast cancers (42% reduction; 95% CI: 12, 62; \( P = 0.01 \)) compared with tamoxifen (ATAC Trialists’ Group, 2005). The advantages of anastrozole over tamoxifen were further improved in the hormone receptor-positive population (ATAC Trialists’ Group, 2005).

In contrast to tamoxifen, anastrozole does not mediate its effects through the oestrogen receptor, and therefore may confer tolerability advantages to women particularly in relation to its effects on the endometrium. Notably, the endometrial sub-protocol of the main ATAC trial is the first prospectively designed study to directly compare the effects of anastrozole and tamoxifen on the endometrium during the treatment of EBC. This sub-protocol was initiated to assess the background incidence of endometrial abnormalities in an untreated population of postmenopausal women with EBC, and to evaluate prospectively the incidence and nature of subsequent intra-uterine changes occurring de novo following endocrine therapy in a subgroup of patients participating in the main trial. The baseline data for this sub-protocol have been published elsewhere (Duffy et al., 2003). Here we report endometrial histology and abnormalities in postmenopausal women with EBC after 1 and 2 years of treatment with anastrozole, tamoxifen or the combination. This is the first such prospectively designed study with information on uterine pathology occurring over time in women treated with adjuvant hormonal therapies for breast cancer.

Materials and methods

Patients

Patients for this sub-protocol were recruited from selected oncology clinics taking part in the main ATAC trial. Of the 381 clinics participating in the ATAC trial, 31 were identified as having the facilities and expertise to perform the investigations for the endometrial sub-protocol. The eligibility criteria for the main ATAC trial are published in full elsewhere (ATAC Trialists’ Group, 2002). Briefly, the patient population were post-menopausal women with invasive operable breast cancer, who were candidates to receive adjuvant hormonal therapy. To be eligible for this endometrial sub-protocol, patients were also required to satisfy four additional inclusion criteria as follows: no previous tamoxifen; no previous or planned hysterectomy; no previous endometrial ablation; and documented written informed consent to participate in the endometrial sub-protocol.

There were no exclusion criteria in addition to that of the main study for this sub-protocol.

Study design

This randomized, double-blind, multicentre trial was approved by recognized Ethics Committees and Institutional Review Boards, and was designed and run by an independent Steering Committee (SC) and International Co-ordinating Committee (ICC), to comply with the ethical principles of Good Clinical Practice (GCP) as required by the major regulatory authorities, and in accordance with the Declaration of Helsinki.

Patients who met the eligibility criteria for the main ATAC trial were randomized on a 1:1:1 basis, using predetermined computer-generated randomization schemes prepared by the AstraZeneca Biostatistics Group, into one of three treatment groups. Patients in each group received a daily dose of two tablets: anastrozole 1 mg plus tamoxifen placebo; tamoxifen 20 mg plus anastrozole placebo; or anastrozole 1 mg plus tamoxifen 20 mg. The design of the endometrial sub-protocol of the main ATAC trial is shown in Figure 1. Those patients who met the additional criteria to enter this sub-protocol were assessed at entry to the trial (baseline) and at 1 and 2 years after the start of treatment.

The combination treatment arm of the main ATAC trial was closed after the initial analyses at 33 and 47 months of follow-up (ATAC Trialists’ Group, 2002, 2003) because of low efficacy.

Objectives

The primary objective of the endometrial sub-protocol was to assess the incidence of abnormal endometrial histology findings amongst those patients receiving anastrozole 1 mg compared with those receiving tamoxifen 20 mg. Secondary objectives of the trial were to assess:

(i) the non-inferiority of this incidence between the tamoxifen group and the combination group (if non-inferiority was not concluded, no further analyses were to be performed); (ii) the background endometrial abnormality rate at trial entry (baseline); (iii) the incidence of specific endometrial abnormalities; and (iv) the requirement of medical intervention for endometrial abnormalities.

Assessments

Endometrial abnormalities were assessed using a combination of transvaginal ultrasonography (TVS), hysteroscopy, and pipelle sampling at baseline and after 1 year and 2 years of treatment. Three assessments were made using TVS: endometrial thickness, uterine dimensions and uterine ultrasound findings (polyps and fibroids). Endometrial thickness (mm) was measured in the longitudinal section of the midline plane at the widest point (‘double-sandwich’ technique). Uterine dimensions (mm) included longitudinal diameter (measured from the outer aspect of the uterine fundus), depth (longitudinal section at the widest diameter) and width (transverse section at the widest diameter). If polyps were detected using ultrasound, the number of polyps, maximum dimension (mm) and site were recorded; if fibroids were detected, they were similarly recorded.

Hysteroscopy was used to assess whether the endometrium was normal or atrophic, or abnormal. Abnormal findings included polyps, fibroids and ‘suspicious’ endometrium (appearances suggestive of cancer).

Pipelle sampling was used to obtain endometrial samples suitable for histopathological assessment. Histopathological findings for each patient were recorded in a standard format as one or more of the following: inactive/atrophic; proliferative; simple hyperplasia; complex hyperplasia; atypical hyperplasia (low or high grade); fibroid; carcinoma (including grade 1, 2 or 3); secretory; menstrual; ‘other’ findings.
Baseline screening

At the baseline assessment, hysteroscopy and TVS were performed prior to randomization of the patient. Any polyps identified were removed; fibroids were left intact. Patients with endometrial hyperplasia identified at baseline continued in the main ATAC trial but were subsequently withdrawn from this endometrial sub-protocol. Patients found to have endometrial carcinoma at baseline hysteroscopy, performed prior to randomization, were excluded from entering the main ATAC trial and hence from entering this sub-protocol.

Statistical analyses

Primary endpoints of this sub-protocol were overall incidence of histologically confirmed endometrial abnormalities, analysed using logistic regression and the comparison of anastrozole with tamoxifen, presented as an odds ratio (OR) with a two-sided 95% confidence interval (CI) and P-value. Secondary endpoints were the incidences of specific abnormalities, background abnormality rates and the frequency of medical interventions for abnormalities. The incidence of specific abnormalities was analysed, where the incidence was ≥5%, using Fisher’s exact tests. P-values were presented to compare treatment
groups. Background abnormality rates and frequency of medical intervention for abnormalities were both expressed as absolute values and percentages. Sample size calculations estimated that ≥500 patients should be recruited into this sub-protocol to provide sufficient power for statistical analyses.

Results

Baseline demographics

A total of 285 patients was recruited into this sub-protocol, from a total of 31 centres taking part in the main ATAC trial (ATAC Trialists’ Group, 2002). This study was unable to reach its target recruitment of 500 women as the main ATAC trial achieved its target event rate (and therefore stopped recruiting) before recruitment to the sub-protocol was completed. Six patients were withdrawn because they did not receive trial therapy and eight were withdrawn due to abnormalities at baseline. The remaining 271 patients were treated and did not have baseline endometrial abnormalities (primary analysis population). A total of 87 patients had incomplete information for the 2 year analyses: 69 were withdrawn and in 18 the procedure failed or was omitted. The corresponding numbers for the 1 year analyses were: 62 patients with incomplete information, of whom 48 withdrew and 14 had failed/omitted procedure. Hence, data are available for 209 patients up to year 1 and 184 patients up to year 2. The overall withdrawal rates were similar across the three treatment groups. An overview of the number of patients included in the analyses is shown in Figure 2.

Treatment groups were well balanced in terms of demographics and tumour characteristics (Table I). An exception was that the anastrozole group contained a higher number of patients receiving prior HRT than the tamoxifen and combination groups (Table I). Of the 271 patients remaining in the primary analysis population, 90 (33.2%) were node positive, 188 (69.4%) had a tumour ≤2 cm maximum diameter and 209 (77.1%) were hormone receptor positive. A number of patients with negative or unknown hormone receptor status

![Figure 2](https://academic.oup.com/humrep/article-abstract/21/2/545/613995/121254561385)
were included because, at the time the ATAC trial was initiated, it was thought that adjuvant hormonal therapy might also confer some benefit to patients who had hormone receptor-negative tumours (ATAC Trialists’ Group, 2002). In addition, hormone receptor status was not routinely assessed in some of the countries participating in the ATAC trial and, therefore, a number of tumours with unknown receptor status at randomisation were subsequently found to be hormone receptor-negative (ATAC Trialists’ Group, 2002).

Endometrial abnormalities at baseline

The baseline incidence of endometrial abnormalities confirmed histopathologically was 9.0% (24 of the 268 patients assessed at baseline), the commonest abnormalities being polyps (no atypia), occurring in 23 of the 268 patients (background incidence of polyps = 8.5%).

Change in endometrial thickness

No change in ultrasound-measured median endometrial thickness from baseline (3.0 mm) was seen in patients treated with anastrozole after 2 years (endometrium remained <5 mm thick), while median endometrial thickness increased with tamoxifen from 3.8 mm at baseline to 6.5 mm after 1 year, and to 7.0 mm after 2 years (Figure 3).

Endometrial thickening was observed to similar degrees in both the tamoxifen and combination arms (Figure 3). For the combination group, median endometrial thickness was 3.0 mm at baseline and had increased to 7.0 mm after both 1 and 2 years of treatment.

Endometrial abnormalities during the study

The overall number of endometrial abnormalities at years 1 and 2 were numerically lower in the anastrozole group than in the tamoxifen group, although these differences were not statistically significant (at 1 year: 4 versus 7 abnormalities; OR: 0.54; 95% CI: 0.147, 1.971; *P* = 0.35; at 2 years: 6 versus 10 abnormalities; OR: 0.44; 95% CI: 0.146, 1.314; *P* = 0.14) (Table II). The majority of endometrial abnormalities occurred during the first year of treatment (Table II).

The overall number of endometrial abnormalities at years 1 and 2 were numerically higher in the combination group than in the tamoxifen group, again these differences were not statistically significant (at 1 year: 10 versus 7 abnormalities; OR: 1.69; 95% CI: 0.597, 4.812; *P* = 0.32; at 2 years: 16 versus 10 abnormalities; OR: 1.64; 95% CI: 0.670, 4.027; *P* = 0.28) (Table II). Non-inferiority was not concluded, and no further analyses were performed.

Of those patients with complete information, the proportion of patients exhibiting endometrial histopathology were 5.1, 10.1 and 16.1% in the anastrozole, tamoxifen and combination groups respectively at 1 year, and 8.7, 17.9 and 27.1% respectively at 2 years.

Specific endometrial abnormalities

The majority of abnormalities in all treatment groups were polyps (no atypia or atypia unknown) with no significant differences between groups at either the 1 or 2 year treatment duration (Figures 4a and b).

Medical intervention for endometrial abnormalities

Similarly, the incidence of patients requiring medical intervention (polypectomy in all cases) for endometrial abnormalities in the anastrozole group was numerically lower than that seen in the tamoxifen and combination groups at both 1 and 2 years (Table III).
There was one serious abnormality (atypical hyperplasia in the tamoxifen group), which occurred after 1 year of treatment (Table II; Figure 4a and b).

Discussion

This is the first double-blind, randomized study to prospectively investigate endometrial abnormalities with tamoxifen versus anastrozole treatment from baseline right through to 5 years. Here we report data for the first 2 years of treatment and show for the first time that anastrozole is less likely than tamoxifen to cause endometrial abnormalities during treatment of post-menopausal women with EBC.

We report no change from baseline in endometrial thickness after 2 years in patients treated with anastrozole, whereas endometrial thickening did occur in patients treated with tamoxifen or the combination. This finding is consistent with safety data from the main ATAC trial, which showed that the incidence of endometrial cancer in patients being treated with anastrozole was significantly lower compared with tamoxifen \[5/3092 (0.2\%) \text{ with anastrozole versus 17/3094 (0.8\%) with tamoxifen; } P = 0.02\] (ATAC Trialists’ Group, 2005), and was comparable or lower than the levels of endometrial cancer seen in a normal age-matched population (Duffy and Greenwood, 2003). A significant increase in endometrial thickness (Schmidt and Romer, 2002) has previously been observed with tamoxifen-treated patients when compared with patients not receiving tamoxifen (Cohen et al., 1994; Lindahl et al., 1997), and the increase in endometrial proliferation has been shown to be associated with duration of tamoxifen treatment (Decensi et al., 1996; Bergman et al., 2000).

Incidences of endometrial abnormalities in this sub-protocol were also numerically lower in patients treated with anastrozole compared with tamoxifen, although not statistically significant. These data are also consistent with reports from the main ATAC trial, where anastrozole, compared with tamoxifen, was shown to lead to lower incidences of the symptoms associated with endometrial abnormalities [vaginal bleeding: 167/3092 (5.4\%) with anastrozole versus 317/3094 (10.2\%) with tamoxifen; \(P < 0.0001\)] (ATAC Trialists’ Group, 2005). The results of this endometrial sub-protocol also showed that most endometrial abnormalities arose within the first year, irrespective of the treatment received, indicating that patients should be monitored more closely during the first year of therapy.

Although no significant differences between anastrozole and tamoxifen were seen in this sub-protocol, this is likely to be because the number of patients recruited was insufficient based on the original power calculations. Recruitment into the main ATAC trial was rapid and target patient numbers were reached.

Table II. Overall number of endometrial abnormalities after 1 and 2 years of treatment

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>Hysteroscopy/histopathology</th>
<th>Treatment first received ([n (%)])</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anastrozole ((n = 97))</td>
<td>Tamoxifen ((n = 89))</td>
</tr>
<tr>
<td></td>
<td>Abnormal</td>
<td>Normal</td>
</tr>
<tr>
<td>1 year</td>
<td>4 (4.1)</td>
<td>7 (7.9)</td>
</tr>
<tr>
<td></td>
<td>74 (76.3)</td>
<td>62 (69.7)</td>
</tr>
<tr>
<td></td>
<td>Incomplete information(^b)</td>
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<tr>
<td></td>
<td>19 (19.6)</td>
<td>20 (22.5)</td>
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<td></td>
<td>6 (6.2)</td>
<td>10 (11.2)</td>
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<tr>
<td>2 years</td>
<td>63 (64.9)</td>
<td>46 (51.7)</td>
</tr>
<tr>
<td></td>
<td>Incomplete information(^b)</td>
<td>28 (28.9)</td>
</tr>
</tbody>
</table>

\(^a\)Includes one serious abnormality (atypical hyperplasia).

\(^b\)Failed/omitted/withdrawn/no visit.
before the required numbers were enlisted into this sub-protocol. Despite this, recruitment into the endometrial sub-protocol was also closed when 285 patients had been recruited.

It is possible that the lack of a statistically significant difference in the incidence of endometrial abnormalities in the anastrozole and tamoxifen groups may have been related to differences in the prior use of HRT (49.5 versus 31.5% of the patients in the two groups, respectively). However, conflicting data in the literature regarding the effect of HRT on endometrial cancer risk make it difficult to draw firm conclusions—some studies suggest an increased risk with any type of HRT (Newcomb and Trentham-Dietz, 2003; Welnicka-Jaskiewicz and Jassem, 2003), others suggest an increased risk with estrogen-only HRT but not with oestrogen plus progesterone (Nelson et al., 2002; Rossouw et al., 2002), and further studies suggest no increased risk with any type of HRT (Beral et al., 2002) or even a reduced risk with combined oestrogen plus progesterone HRT (Gambacciani et al., 2003).

The formation of *de novo* polyps in the anastrozole group was unexpected. Polyp formation has been thought to be due to proliferation, which in turn is estrogen driven. As anastrozole provides a more complete estrogen-deficient environment, this observation questions the link between polyp formation and estrogen. It is possible that polyp formation may be determined by other influences, such as a genetic pre-disposition. A significant increase in endometrial polyps after 1–2 years of tamoxifen treatment has previously been shown (11.8% before treatment versus 29.4% after 1–2 years of treatment, OR = 13; 95% CI: 7.9–18.1) (Andia et al., 2000), and such polyps may be an important intermediate step in endometrial carcinogenesis (Nuovo et al., 1989; Ismail, 1994).

Incidence of patients requiring medical intervention for endometrial abnormalities in this sub-protocol were also numerically lower in patients treated with anastrozole compared with tamoxifen. It is unclear why a higher proportion of patients who were treated with tamoxifen required medical intervention for their endometrial abnormalities than those who were treated with anastrozole. This issue will be addressed in a later publication on gynaecological events in the main ATAC trial but it may be related to the symptoms experienced by patients who received tamoxifen. It is again consistent with the lower incidence of vaginal bleeding for anastrozole than for tamoxifen in the main ATAC trial, since the majority of vaginal bleeding events warrant follow-up endometrial investigation. Endometrial examinations cause anxiety for the patient, and are invasive, costly and resource-intensive procedures. Thus the reduced incidence of the requirement for medical intervention following anastrozole treatment is important, both with respect to the psychological well-being of patients already faced with having breast cancer and from a health economics perspective.

In summary, this sub-protocol has found fewer endometrial abnormalities arising *de novo* during 2 years of treatment with anastrozole compared with tamoxifen. This study also found that endometrial thickness, as a surrogate marker of endometrial proliferation, remained consistently <5 mm in the anastrozole group. In addition, there was less need for medical intervention. Finally, the majority of endometrial abnormalities occurred in the first year of treatment. These findings are consistent with the superior safety profile and the lower risk of endometrial cancer with anastrozole compared with tamoxifen as demonstrated in the main ATAC trial.

**Conflict of interest statement**

S.Duffy, A.R.Bianco and M.Cobion have all received travel awards from AstraZeneca to attend the ATAC trial steering committee meetings. T.Jackson has received funding from AstraZeneca to present data at several conferences. M.Lansdown has accepted funding from AstraZeneca to attend accredited postgraduate meetings and his department has received financial support for trials approved by the ethics committee. S.Pollard holds a contract with AstraZeneca for operational management and to support some of the monitor- ing of the trial. G.Clack is an employee of AstraZeneca.

**References**


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Table III. Medical intervention for endometrial abnormalities

<table>
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<tr>
<th>Treatment duration</th>
<th>Intervention</th>
<th>Treatment first received</th>
<th>Anastrozole</th>
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<td></td>
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<td>Total patients with abnormality</td>
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<td>10 (16.1)</td>
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<td>8 (13.6)</td>
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<td>10 (17.9)</td>
<td>16 (27.1)</td>
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Appendix A. ATAC trial steering committee membership

Professor J.Adams: University of Manchester, Manchester, UK; Professor M.Baum: University College London (UCL), London, UK; Professor A.R.Bianco: Universita Degli Studi Di Napoli Federico II, Napoli Italy; Dr A.Buzdar: The University of Texas, M.D.Anderson Cancer Center, Houston, USA; Professor D.Cella: Northwestern University, Evanston, Illinois, USA; Dr M.Cobin: Institut Bordet, Bruxelles, Belgium; Professor R.Coleman: Cancer Research Centre, Weston Park Hospital, Sheffield, UK; Dr M.Constena: Hospital Montecelo, Pontevedra, Spain; Professor J.Cuzick: Cancer Research UK, London, UK; Professor Dr W.Distler: Frauenklinik Carl Gustav Carus Universitat Dresden, Dresden, Germany; Professor M.Dowsett: The Royal Marsden Hospital, London, UK; Mr S.Duffy: St James’s University Hospital, Leeds, UK; Professor R.Eastell: University of Sheffield, Sheffield, UK; Professor L.J.Fallowfield, University of Sussex, Brighton, UK; Professor J.Forges: Newcastle Mater Misericordiae Hospital, NSW, Australia; Professor W.D.George: Beatson Oncology Centre, Western Infirmary, Glasgow, UK; Sister J.Gray: Belfast City Hospital, Belfast, UK; Dr J.-P.Guastalla: Centre Leon Bérard, Lyon, France; Mr R.Hellmund, Mr G.Hoctin-Boes: AstraZeneca Pharmaceuticals, Wilmington, USA; Mrs J.Houghton, Dr N.Williams: Clinical Trials Group of the Department of Surgery, UCL, London, UK; Professor A.Howell: Christie Hospital, Manchester, UK; Professor Dr J.G.M.Klijn: Dr Daniel den Hoed Kliniek and University Hospital, Rotterdam, Rotterdam, The Netherlands; Dr G.Y.Locke: Evanston Northwestern Healthcare, Northwestern University Feinberg School of Medicine, Evanston, IL, USA; Dr J Mackey: Cross Cancer Institute, Edmonton, Alberta, Canada; Professor R.E.Mansel: Professor of Medicine, University of NSW, Sydney, Australia; Professor M.Nabholtz: Hartman Oncology Institute, Levallois-Perret, France; Dr T.Nagykalaia: Uzsozi U.Hospital, Budapest, Hungary; Dr A.Nicolucci: GIVIO Co-coordinating Centre, Consorzio Mario Negri Sud, Centro Di Ricerche Farmacologici, E.Biomedichi, Chieta, Italy; Dr U.Nylén: Radiumhemmet, Karolinska Sjukhuset, Stockholm, Sweden; Mr R.Sainsbury: University College London (UCL), London, UK; Mr F.Sapunar, Dr V.J.Suarez-Mendez: AstraZeneca Pharmaceuticals, Macclesfield, UK; Professor J.S.Tobias: The Meyerstein Institute of Clinical Oncology, Middlesex Hospital, London, UK.

Appendix B. Investigators in the ATAC endometrial sub-protocol

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Appendix C. Additional ATAC trial committees and collaborative/operational groups

International Project Team
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Data Monitoring Committee
Dr M.Buyse: International Institute for Drug Development (IDDI), Brussels, Belgium; Professor J.Cuzick (Independent statistician), Mr C.Wale: Cancer Research UK, London, UK; Dr R.Margo lese: McGill University, The Sir Mortimer B.Davis Jewish General Hospital, Montre al, Quebec, Canada; Professor J.J.Body: Institute J.Bordet, Bruxelles, Belgium.

Collaborative/Operational Groups
J.F.Forbes (Group Co-ordinator), J.K.Wakeham (Study Coordinator): Australian New Zealand Breast Cancer Trials Group Operations Office; S.de Placido (Study Co-ordinator), C.Car lomagno (Study Co-ordinator): Universita Degli Studi Di Napoli Federico II, Italy; A.Nicolucci (Group Co-ordinator), M.Belfiglio (Study Co-ordinator), M.Valentini (Study Co-ordinator): GIVIO Group, Consorzio Mario Negri Sud, Italy; E.Foster (Principal Trial Co-ordinator and CCTT contact): ISD Cancer Clinical Trials Team, Edinburgh, UK, Liz.Foster@isd.csa.scot.nhs.uk; C.Lacey (Trial monitor): North West Breast Group, Burnley, Lancashire, UK; S.Pollard (Head of Pharmaceutical Collaboration): Clinical Trials Research Unit, University of Leeds, Leeds, UK; J.Houghton (Senior Lecturer in Clinical Trials and CTG contact), N.Williams (Trial Co-ordinator): Clinical Trials Group of the Department of Surgery, UCL, London, UK, j.houghton@ctg.ucl.ac.uk.