Articles

Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial

*The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trialists' Group**

Summary

Background In the adjuvant setting, tamoxifen is the established treatment for postmenopausal women with hormone-sensitive breast cancer. However, it is associated with several side-effects including endometrial cancer and thromboembolic disorders. We aimed to compare the safety and efficacy outcomes of tamoxifen with those of anastrozole alone and the combination of anastrozole plus tamoxifen for 5 years.

Methods Participants were postmenopausal patients with invasive operable breast cancer who had completed primary therapy and were eligible to receive adjuvant hormonal therapy. The primary endpoints were disease-free survival and occurrence of adverse events. Analysis for efficacy was by intention to treat.

Findings 9366 patients were recruited, of whom 3125 were randomly assigned anastrozole, 3116 tamoxifen, and 3125 combination. Median follow-up was 33·3 months. 7839 (84%) patients were known to be hormone-receptor-positive. Disease-free survival at 3 years was 89·4% on anastrozole and 87·4% on tamoxifen (hazard ratio 0·83 [95% CI 0·71–0·96], p=0·013). Results with the combination were not significantly different from those with tamoxifen alone (87·2%, 1·02 [0·89–1·18], p=0·8). The improvement in disease-free survival with anastrozole was seen in the subgroup of hormone-receptor-positive patients, but not the receptor-negative patients. Incidence of contralateral breast cancer was significantly lower with anastrozole than with tamoxifen (odds ratio 0·42 [0·22–0·79], p=0·007). Anastrozole was significantly better tolerated than tamoxifen with respect to endometrial cancer (p=0·02), vaginal bleeding and discharge (p<0·0001 for both), cerebrovascular events (p=0·0006), venous thromboembolic events (p=0·0006), and hot flushes (p<0·0001). Tamoxifen was significantly better tolerated than anastrozole with respect to musculoskeletal disorders and fractures (p<0·0001 for both).

Interpretation Anastrozole is an effective and well tolerated endocrine option for the treatment of postmenopausal patients with hormone-sensitive early breast cancer. Longer follow-up is required before a final benefit:risk assessment can be made.

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See Commentary page 2126

*Members listed at end of paper

Correspondence to: ATAC Secretariat, C/o Cancer Research UK and UCL Cancer Trials Centre, Stephenson House, 158–160 North Gower Street, London NW1 2ND, UK
(e-mail: j.houghton@ctc.ucl.ac.uk)

Introduction

Many breast cancers depend on oestrogens for their continued growth. Depriving the tumour of this stimulus is an established method of treating the disease.[1–2] In the adjuvant setting, tamoxifen is the established treatment for women with hormone-sensitive disease. This drug has substantial benefits in terms of disease-free and overall survival, and can reduce rates of contralateral breast cancer compared with control or placebo.[3,4] Furthermore, the continuing Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overviews have provided definitive confirmation of the value of tamoxifen. The most recently published analysis showed that, in patients with hormone-receptor-positive disease, the odds of recurrence and death were reduced by 47% and 26%, respectively, after about 5 years of treatment.[5]

In addition to its established antitumour efficacy, tamoxifen therapy provides other beneficial effects—eg, protection against bone loss in postmenopausal women[6]—that relate to the partial oestrogen-agonist action of the drug. However, these partial agonist effects are also associated with several clearly defined risks. Although tamoxifen is generally well tolerated, lengthy use of this agent is associated with gynaecological complications, including proliferative endometrial abnormalities in postmenopausal women. An increased incidence of endometrial cancer has been reported in association with tamoxifen treatment, and the level of risk seems to be time-dependent and dose-dependent.[7] Many studies have found a two to four times higher relative risk of developing endometrial cancer in women taking tamoxifen than in an age-matched population.[5,8] Most cases of endometrial cancer after tamoxifen treatment are low-grade stage 1 tumours,[9] but a small proportion are high-grade sarcomas.[10] Other side-effects related to the oestrogenic properties of tamoxifen include an increased risk of thromboembolic disorders, especially when given in combination with chemotherapy.[11,12]

In the mid-1990s, the third-generation aromatase inhibitors became available, initially for the treatment of advanced breast cancer in postmenopausal women for whom tamoxifen therapy fails. Aromatase inhibitors are a class of compounds that inhibit the synthesis of oestrogen from androgens in postmenopausal women. Anastrozole (Arimidex), which became available in 1995, is a potent, orally active, highly selective, non-steroidal aromatase inhibitor that substantially reduces oestrogen concentrations in postmenopausal women with breast cancer.[13]

In advanced disease, anastrozole is well tolerated and has a significant survival advantage over megestrol acetate as second-line treatment.[14] It was also shown to be better than tamoxifen with respect to time to progression when used as first-line treatment for advanced breast cancer in a

North American trial,[15] and to be at least as effective as tamoxifen with respect to time to progression in a second, larger international trial.[16] A combined analysis of the two trials showed anastrozole to be at least as good as tamoxifen in the overall population, and to result in a significantly increased time to progression compared with tamoxifen in patients with known hormone-receptor-positive disease.[17] Additionally, anastrozole led to reduced incidences of thromboembolic disease and vaginal bleeding in these studies.

Thus, the place of tamoxifen as the gold standard for the first-line treatment of postmenopausal women with advanced hormone-sensitive breast cancer has recently been challenged by anastrozole. The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial compared the established adjuvant treatment, tamoxifen, with anastrozole alone and in combination with tamoxifen as adjuvant treatment for postmenopausal women with early, operable breast cancer. The trial was designed to answer the following questions: (1) Is anastrozole at least as effective as tamoxifen in postmenopausal women with early operable breast cancer? (2) Does anastrozole offer any safety or side-effect benefits over tamoxifen in this group of patients? (3) Could a combination of anastrozole plus tamoxifen offer additional efficacy or safety benefits over tamoxifen alone? Inclusion of a combination group allowed investigation of any possible additive effects through the use of two drugs with different modes of action. Here we report the first efficacy and safety results of the ATAC trial.

Patients and methods

Patients

Eligible patients were postmenopausal women with histologically proven operable invasive breast cancer who had completed primary surgery and chemotherapy (where given), and were candidates to receive hormonal adjuvant therapy. Patients were defined as being postmenopausal if they satisfied one or more of the following criteria: having had a bilateral oophorectomy; aged more than 60 years; or aged 45–59 years with an intact uterus and amenorrhoeic for at least 12 months. If a patient had been amenorrhoeic for less than 12 months (including patients who had undergone a hysterectomy and those who had received hormone replacement therapy [HRT] or who had been rendered amenorrhoeic by chemotherapy), follicle-stimulating-hormone (FSH) concentrations within the postmenopausal range were required for eligibility.

At the time the ATAC trial was started, patients with negative or unknown hormone-receptor status were included because hormone-receptor-negative patients were thought to derive benefit from adjuvant therapy with a hormonal agent.[18] Since assessment of hormone-receptor status was not routinely available in some countries, many of the patients whose tumours were later found to be hormone-receptor negative had tumours of unknown receptor status at the time of randomisation. Nevertheless, the protocol foresaw the need to analyse the treatment effect specifically in patients with hormone-receptor-positive tumours.

Patients were ineligible if there was any clinical evidence of metastatic disease; if chemotherapy was started more than 8 weeks after surgery or completed more than 8 weeks before starting randomised treatment (neoadjuvant chemotherapy was not allowed) or, in patients not receiving chemotherapy, if primary surgery was completed more than 8 weeks before starting randomised treatment; or if they had received hormonal therapy for breast-cancer prevention or for adjuvant treatment of breast cancer (except if tamoxifen treatment was started before surgery and received for less than 29 days, or if hormonal therapy was received before surgery in the context of a formal trial previously approved by the Steering Committee). Patients were not eligible if they were unwilling to stop any hormonal drug including HRT; if they had a previous history of invasive malignant disease (breast cancer at any time, other malignant disorders within the past 10 years excluding squamous or basal-cell carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied); or if the patient had any severe concomitant disease which would place the patient at unusual risk or confound the results of the trial.

Patients were included only after the trial had been explained to them, they had had time to consider the written information leaflet, and had given their written informed consent to join the trial. The protocol was approved by the appropriate local regulatory and ethics authorities for each participating centre before enrolment of patients began. The trial was conducted in accordance with the Declaration of Helsinki (1996 revision) and under the principles of good clinical practice, as laid out in the International Conference on Harmonisation document *Good Clinical Practice Consolidated Guideline*.

Procedures

The trial was designed to test two hypotheses: that anastrozole was non-inferior or superior to tamoxifen and that the combination of anastrozole and tamoxifen was superior to tamoxifen alone as adjuvant therapy in postmenopausal patients with early breast cancer. The primary objectives of the trial were efficacy against breast cancer and safety. The primary endpoint was disease-free survival (defined as the time to the earliest occurrence of local or distant recurrence, new primary breast cancer, or death from any cause). Secondary endpoints were time to a recurrence (including new contralateral tumours, but not including patients who had died from non-breast-cancer causes before recurrence) and incidence of new contralateral primary breast tumours. Distant recurrence and overall survival were also secondary endpoints, but there were insufficient events at this stage for a formal analysis.

Because of the international nature of the trial, randomisation services were offered at 23 sites around the world so that a service was offered within the local time zone. The randomisation schedule (block size 6) was generated centrally by computer, distributed to the randomisation centres, and the central copy was secured. Patients were randomised in a 1:1:1 ratio to receive active anastrozole plus tamoxifen placebo; active tamoxifen plus anastrozole placebo; or active anastrozole plus active tamoxifen. Tamoxifen was given as 20 mg tablets and anastrozole as 1 mg. Patients receiving chemotherapy were randomised only when blood counts were within the normal range after the last course of treatment. Therefore, patients who received chemotherapy began hormonal therapy on average 6–8 months after diagnosis.

Surgery, radiotherapy, and chemotherapy were carried out according to local practice policies. Patients could start trial therapy while receiving radiotherapy.

Drugs that affect sex-hormone status or were known to prevent recurrence of the disease could not be used after randomisation if the patient remained on trial therapy. Patients who reported severe menopausal symptoms and who were willing to continue trial therapy were given progestins for 3–6 months initially. If this treatment failed to control the symptoms, HRT or oestrogen creams could be prescribed and trial therapy continued. Symptoms

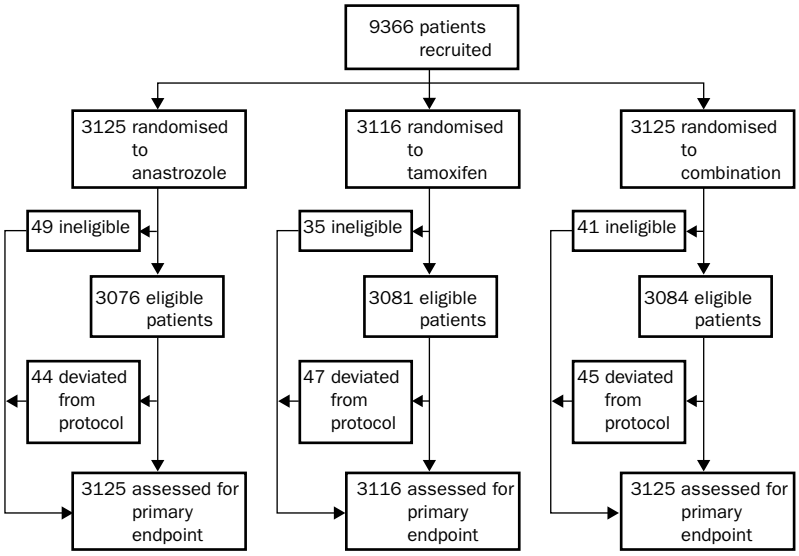

Figure 1: **Trial profile**

and treatment were reported on appropriate trial documentation. Less than 1% of patients received systemic HRT, and about 2% received topical creams. There were no major differences between treatment groups with respect to the numbers who received these treatments.

Patients were scheduled for assessments at entry, 3 months, and 6 months; thereafter assessments were scheduled every 6 months up to 5 years, and then annually for up to 10 years. Confirmation of recurrence required histology or cytology (for locoregional disease) or imaging for distant disease. Site and date of the investigation that led to a confirmation were recorded. Five deaths attributed by the investigator to breast cancer occurred without prior notification of recurrence (one in the tamoxifen-alone group, two in the anastrozole-alone group, and two in the combination group). These have been ascribed as distant recurrences at the date of death.

Investigators were required to ask each patient at every visit whether or not any adverse events had been experienced. These events were recorded on the trial case-report forms, but no prespecified checklists were used. Immediate reporting was required for serious adverse events. Trial therapy was stopped if the patient refused to continue, if recurrence was confirmed, or on the recommendation of the investigator.

Unmasking of treatment assignment was done through the randomisation centres. If knowledge of the allocated treatment was required, a short questionnaire was completed over the telephone to determine the reason before breaking the code for any individual trial participant.

	Anastrozole (n=3125)	Tamoxifen (n=3116)	Combination (n=3125)
Demographics			
Age (mean [SD], years)	64·1 (9.0)	64·1 (9.0)	64·3 (9.1)
Weight (mean [SD], kg)	70·8 (14.1)	71·1 (14.2)	71·3 (14.3)
Height (mean [SD], cm)	160·9 (6.9)	160·7 (6.9)	160·5 (6.9)
BMI (mean [SD], kg/m^2)	27·4 (5.3)	27·6 (5.4)	27·7 (5.3)
Previous HRT	1114 (35·6%)	1103 (35·4%)	1103 (35·3%)
Hysterectomy	876 (28·0%)	864 (27·7%)	862 (27·6%)
Nodal status			
N+(1–3)	766 (24·5%)	762 (24·4%)	759 (24·3%)
N+(≥4)	326 (10·4%)	283 (9·1%)	286 (9·2%)
Negative	1876 (60·0%)	1915 (61·5%)	1904 (60·9%)
Unknown	157 (5·0%)	154 (4·9%)	175 (5·6%)
Tumour size			
≤2 cm	1996 (63·9%)	1959 (62·9%)	2004 (64·1%)
>2–5 cm	1018 (32·6%)	1066 (34·2%)	1027 (32·9%)
>5 cm	85 (2·7%)	69 (2·2%)	73 (2·3%)
Tumour grade			
Well differentiated	651 (20·8%)	638 (20·5%)	663 (21·2%)
Moderately differentiated	1463 (46·8%)	1488 (47·8%)	1455 (46·6%)
Poorly differentiated/ undifferentiated	740 (23·7%)	727 (23·3%)	741 (23·7%)
Cannot be assessed	267 (8·5%)	260 (8·3%)	264 (8·4%)
Hormone-receptor status			
Positive	2617 (83·7%)	2598 (83·4%)	2624 (84·0%)
Negative	258 (8·3%)	272 (8·7%)	238 (7·6%)
Other	250 (8·0%)	240 (7·9%)	263 (8·4%)
Primary treatment			
Mastectomy	1494 (47·8%)	1474 (47·3%)	1502 (48·1%)
Radiotherapy	1978 (63·3%)	1946 (62·5%)	1936 (62·0%)
Chemotherapy	698 (22·3%)	647 (20·8%)	651 (20·8%)
Tamoxifen before surgery	50 (1·6%)	51 (1·6%)	53 (1·7%)

BMI=body-mass index; HRT=hormone replacement therapy.

Table 1: **Baseline characteristics of patients, tumours, and primary treatment**

Statistical analysis

The primary endpoint of disease-free survival was used to assess sample size. For non-inferiority to be concluded between anastrozole and tamoxifen, 352 events per group were required for a greater than 90% power. Non-inferiority was defined as the ruling out of a hazard ratio greater than 1·25 on the basis of the 90% CI. To show a reduction of 20% in event rates by anastrozole alone or the combination versus tamoxifen alone (superiority), 80% power was achievable at a 5% significance level with the same number of events. On the basis of these estimates, the observed recruitment rate, and the event rates from the EBCTCG overview,[5] we estimated that about 9000 patients would need to be recruited.

The data were analysed for disease-free survival on all randomised patients (including protocol violators) on an intention-to-treat basis by use of the log-rank test without adjustment for prognostic factors. Additional analyses were done with Cox's proportional hazards model, adjusted for baseline characteristics. These

	Anastrozole (n=3125)	Tamoxifen (n=3116)	Combination (n=3125)	Total (n=9366)
First events				
Local recurrence	67	83	81	231
Distant recurrence*	158	182	204	544
Contralateral breast cancer	14	33	28	75
Invasive	9	30	23	62
Ductal carcinoma in situ	5	3	5	13
Deaths before recurrence	78	81	70	229
Total	317 (10·1%)	379 (12·2%)	383 (12·3%)	1079 (11·5%)
Events at any time				
Distant recurrence*	180	203	232	615
Deaths after recurrence	122	122	145	389
All deaths	200	203	215	618

*Including five deaths (two on anastrozole, one on tamoxifen, and two on the combination), which were attributed to breast cancer without prior information about recurrence.

Table 2: **Distribution of events**

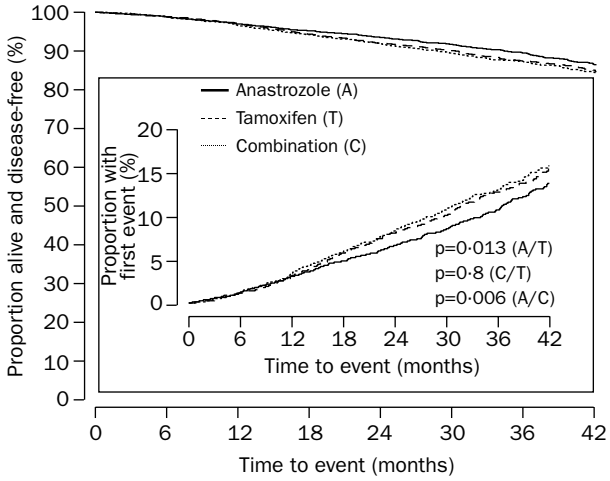

Figure 2: **Kaplan-Meier curves for disease-free survival (ie, all first events) in the intention-to-treat population**
Insert shows same data presented as probability of first event (figures 3, 5, and 6 are in same format). In this and figures 3, 5, and 6 the curves have been truncated at 42 months.

analyses gave similar results to those of the log-rank test and are not reported here.

The major analysis was planned when there were 1056 events. One interim efficacy analysis had been done with a nominal p value of 0·005 when about 528 events had been reported. Therefore the required nominal p value for the main analysis was 0·048 to ensure a true 5% significance level. Analyses were also done to compare anastrozole alone with anastrozole plus tamoxifen in combination. Additional efficacy analyses were done with time to a recurrence as the endpoint.

A positive hormone-receptor status was defined as positivity for either oestrogen receptors or progesterone receptors according to local cutoff values. Receptor status was taken as negative if the tumour was negative for both oestrogen receptors and progesterone receptors, or if it was negative for oestrogen receptors but had an unknown progesterone-receptor status. Any other categories were classified as unknown. In addition to a predefined analysis of results by receptor status, analyses of potential interactions with predictive factors were also undertaken.

Estimates of the treatment effects were expressed as hazard ratios or odds ratios for contralateral breast primary tumours and treatment withdrawals, with associated 95% CIs. Side-effects were summarised according to the hormone treatment first received. Except for other cancers, side-effect events were accrued up to 14 days after stopping treatment. Information on new primary cancers was collected during and after trial treatment (before and after recurrence), but only summarised up to the point of recurrence. The comparisons of prespecified adverse events were based on a simple comparison of proportions, and Fisher's exact two-sided p values were used when necessary.

	Annual recurrence			Hazard ratio (95% CI)		
	Anastrozole (n=3125)	Tamoxifen (n=3116)	Combination (n=3125)	A/T	C/T	A/C
Year						
1	77 (2·49%)	71 (2·30%)	87 (2·82%)	1·08	1·23	0·88
2	78 (2·61%)	127 (4·28%)	123 (4·11%)	0·61	0·96	0·63
3	64 (2·94%)	77 (3·72%)	80 (3·71%)	0·77	1·00	0·77

A=anastrozole; T=tamoxifen; C=combination. Percentage are events per woman-year at risk.

Table 3: **Annual recurrence rates**

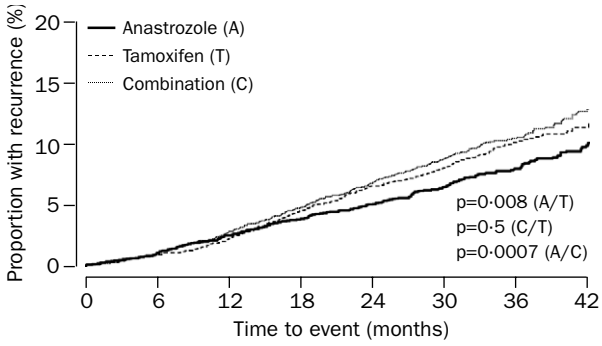

Figure 3: **Probability of recurrence in the intention-to-treat population**

Role of the sponsor

The initial trial plan was developed by the new studies working party of the Cancer Research UK Breast Cancer Trials Group before a sponsor was identified. The management of the trial has subsequently been co-ordinated and supervised by the Steering Committee (SC) and the International Co-ordinating Committee (ICC), with funding and organisational support from the trial sponsor, AstraZeneca. The sponsor was represented in a minority on both committees. The Independent Statistician (JC) who provided information to the independent Data Monitoring Committee at their regular meetings has supervised all data analyses. The interpretation of the analyses in this paper has been by the Writing Group in consultation with both the SC and the ICC.

Results

Patients

9366 women from 381 centres in 21 countries were enrolled between July 12, 1996, and March 24, 2000 (figure 1). Of these women, 125 were found to be ineligible after randomisation (70 were too young or not postmenopausal; 25 had previous cancer; 20 had taken a non-approved drug in the previous 3 months; the rest for a variety of reasons). The results presented below include all randomised patients analysed on an intention-to-treat basis. 5695 (61%) patients were lymph-node negative, 5959 (64%) had a tumour less than or equal to 2 cm in maximum diameter, and 7839 (84%) had either oestrogen-receptor or progesterone-receptor positive tumours. These baseline characteristics, and other patient, tumour, and primary treatment options were well balanced across treatment groups (table 1).

The cutoff date for follow-up was June 29, 2001. Median follow-up was 33·3 months. 7690 (93%) patients without a recurrence had been seen in the previous 6 months. 7876 (84%) patients received more than 99% of allocated treatment.

Efficacy endpoints

1079 first events were recorded (table 2) of which 850 (79%) were recurrences or new contralateral tumours and 229 (21%) were deaths without recurrence.

Disease-free survival was significantly longer for patients on anastrozole alone than for those who received either tamoxifen alone (hazard ratio 0·83 [95% CI 0·71–0·96], p=0·013) or the combination (0·81 [0·70–0·94], p=0·006; figure 2). The combination was not significantly different from tamoxifen alone (1·02 [0·89–1·18], p=0·8). The disease-free survival estimates at 3 years were 89·4%, 87·4% and 87·2% on anastrozole, tamoxifen, and the combination, respectively. In figure 2 (insert), these are presented as event rates of 10·6%, 12·6%, and 12·8%, respectively.

	Number of patients	Hazard ratio (95% CI)
Nodal status		
Negative	5695	1·00
N+(1–3)	2287	1·99 (1·68–2·34)
N+(≥4)	895	5·74 (4·86–6·78)
Unknown	486	1·36 (0·96–1·92)
Tumour size		
≤2 cm	5959	1·00
>2–5 cm	3111	2·91 (2·53–3·36)
>5 cm	227	4·67 (3·49–6·24)
Tumour grade		
Well differentiated	1952	1·00
Moderately differentiated	4406	2·69 (2·02–3·57)
Poor/undifferentiated	2208	6·76 (5·10–8·97)
Other	791	3·62 (2·57–5·09)
Hormone receptor		
Positive	7839	1·00
Negative	768	3·54 (3·00–4·19)
Other	759	1·55 (1·24–1·93)
Age		
<65 years	5137	1·00
≥65 years	4229	1·19 (1·04–1·36)

Table 4: **Hazard ratios for different prognostic factors for breast-cancer events**

There was no major difference in the number of patients who died from any cause before a breast-cancer recurrence (table 2). When these patients were censored at the time of death, the hazard ratio for time to recurrence (including new tumours) was further reduced in the anastrozole group compared with tamoxifen (0·79, [0·67–0·94], p=0·008; figure 3). Anastrozole also showed a greater benefit for this endpoint in comparison with the combination treatment (0·75 [0·63–0·89], p=0·0007). However, no difference was seen between the tamoxifen-alone group and the combination group (1·06 [0·90–1·24], p=0·5).

There was no difference in the annual recurrence rates between patients treated with tamoxifen alone and anastrozole alone in the first year of follow-up, but a difference emerged in the second and third years of follow-up (table 3).

Prognostic factors and subgroups

The standard prognostic factors predicted recurrence as expected (table 4). The recurrence rate was more than three times higher in women with hormone-receptor-negative tumours than in those who were receptor-positive. Interactions of anastrozole or tamoxifen with potential predictive factors are shown in figure 4. The beneficial effect of anastrozole over tamoxifen with respect to time to recurrence was not apparent in patients with receptor-negative disease nor those who had had previous chemotherapy. Longer follow-up is required before any meaningful conclusions can be drawn on the relative efficacy of anastrozole and tamoxifen after adjuvant chemotherapy.

In the hormone-receptor-positive population, the hazard ratios for disease-free survival were 0·78 (0·65–0·93, p=0·005) for anastrozole versus tamoxifen, 0·76 (0·63–0·91, p=0·002) for anastrozole versus the combination, and 1·02 (0·87–1·21, p=0·8) for the combination versus tamoxifen alone (figure 5). The disease-free survival estimates at 3 years were 91·2%, 89·3%, and 88·9%, for anastrozole, tamoxifen, and the combination, respectively.

Time to recurrence (breast-cancer events) in receptor-positive patients was longer in the anastrozole group than the tamoxifen group (0·73 [0·59–0·90], p=0·003; figure 6). There was no significant difference between the tamoxifen and the combination groups (1·09 [0·90–1·32], p=0·4). No difference was found between anastrozole alone and tamoxifen alone for receptor-negative patients (1·13 [0·79–1·61], p=0·5), or patients with tumours of other receptor status (0·77 [0·46–1·29], p=0·3).

Contralateral breast cancer

A striking reduction in primary contralateral breast cancers as a first event was found in the anastrozole group (table 2); when compared with tamoxifen, the odds were reduced by 58% (odds ratio 0·42 [0·22–0·79], p=0·007). The occurrence of primary contralateral breast cancers was similar in both the tamoxifen and the combination groups (0·84 [0·51–1·40], p=0·5).

Most (83%) of the contralateral breast cancers were invasive (table 2), and when the analysis was restricted to

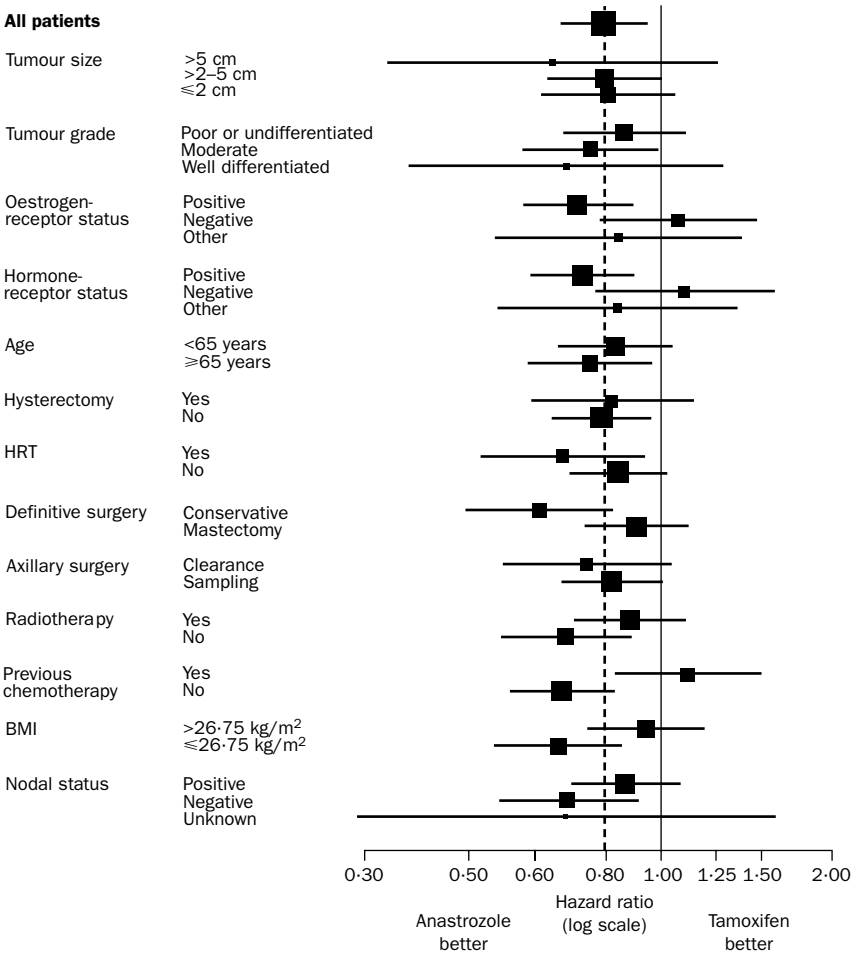

Figure 4: **Subgroup analysis of time to recurrence for tamoxifen versus anastrozole**
Data are hazard ratios and 95% CIs. HRT=hormone replacement therapy. BMI=body-mass index.

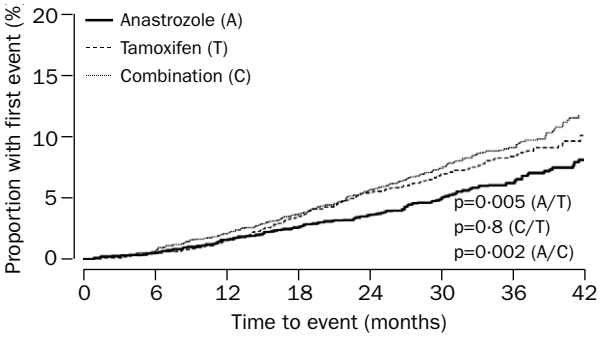

Figure 5: **Probability of a first event in hormone-receptor-positive patients**

these events, the difference between the treatment groups was somewhat larger (odds ratio for anastrozole *vs* tamoxifen 0·30 [0·14–0·63], p=0·001). Findings for the hormone-receptor-positive subgroup were consistent with the overall results (odds ratio for anastrozole *vs* tamoxifen 0·29 [0·13–0·64], p=0·002).

Distant recurrence and breast-cancer deaths

Distant recurrences were recorded in 615 patients, of whom 389 died (breast-cancer deaths). In addition, 229 patients died without a previously reported recurrence (table 2). Formal analyses of anastrozole versus tamoxifen are planned for each of these endpoints after at least 704 such events have occurred in the patients included in these two groups.

Side-effects

The occurrence of predefined side-effects is shown in table 5. In all cases there was no distinguishable difference between the tamoxifen and combination groups. However, in comparison with tamoxifen alone, anastrozole was associated with significant reductions in hot flushes, vaginal discharge, vaginal bleeding, ischaemic cerebrovascular events, venous thromboembolic events (including deep-vein thromboses), and endometrial cancer. By contrast, musculoskeletal disorders and fractures were significantly more common with anastrozole than with tamoxifen. The greatest increase in fractures on anastrozole treatment seemed to be in the spine, and no increase in hip fractures was seen. Other non-prespecified side-effects, notably fibroids and other endometrial findings, were substantially less frequent on anastrozole. Weight gain was similar in the three treatment groups, with the average weight gain being 1·65 kg or 2·5% over 2 years in each group. With the exception of contralateral breast cancers and endometrial cancers, there were no differences between incidences of new primary cancers between the groups (table 6).

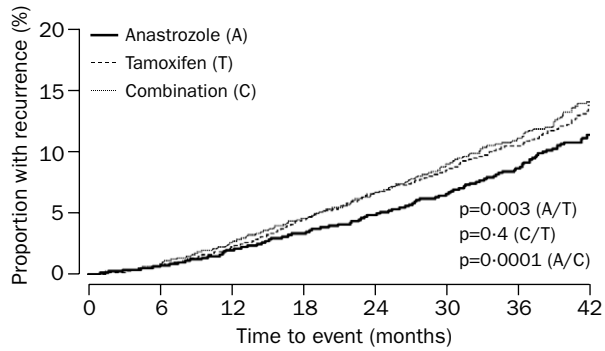

Figure 6: **Probability of recurrence in hormone-receptor-positive patients**

	Anastrozole (n=3092)	Tamoxifen (n=3094)	Combination (n=3097)	p (A *vs* T)
Hot flushes	1060 (34·3%)	1229 (39·7%)	1243 (40·1%)	<0·0001
Nausea and vomiting	324 (10·5%)	315 (10·2%)	363 (11·7%)	0·7
Fatigue/tiredness	483 (15·6%)	466 (15·1%)	435 (14·0%)	0·5
Mood disturbances	480 (15·5%)	469 (15·2%)	482 (15·6%)	0·7
Musculoskeletal disorders	860 (27·8%)	660 (21·3%)	685 (22·1%)	<0·0001*
Vaginal bleeding	138 (4·5%)	253 (8·2%)	238 (7·7%)	<0·0001
Vaginal discharge	86 (2·8%)	354 (11·4%)	357 (11·5%)	<0·0001
Endometrial cancer†	3 (0·1%)	13 (0·5%)	6 (0·3%)	0·02
Fractures	183 (5·9%)	115 (3·7%)	142 (4·6%)	<0·0001*
Hip‡	11 (0·4%)	13 (0·4%)	10 (0·3%)	ND
Spine	23 (0·7%)	10 (0·3%)	14 (0·5%)	ND
Wrist/colles	36 (1·2%)	25 (0·8%)	27 (0·9%)	ND
Ischaemic cardiovascular disease	76 (2·5%)	59 (1·9%)	68 (2·2%)	0·14
Ischaemic cerebrovascular event	31 (1·0%)	65 (2·1%)	51 (1·6%)	0·0006
Any venous thromboembolic events	64 (2·1%)	109 (3·5%)	124 (4·0%)	0·0006
Deep-venous thromboembolic events including PE	32 (1·0%)	54 (1·7%)	63 (2·0%)	0·02
Cataracts	107 (3·5%)	116 (3·7%)	105 (3·4%)	0·6

A=anastrozole; T=tamoxifen; ND=not done; PE=pulmonary emboli. *In favour of tamoxifen. †Excluding patients with hysterectomy at baseline, so denominators were 2228, 2237, and 2240 for anastrozole, tamoxifen, and combination, respectively. Occurrences of endometrial cancer were reported before disease recurrence. Three cases (1 anastrozole, 2 tamoxifen) were reported after stopping treatment, but before recurrence. In addition there were 2 non-endometrial uterine cancers (1, 0, 1, respectively) and 3 vulva cancers (1, 0, 2, respectively). Whether there were any intervening treatments in the time after stopping initial treatment and before recurrence is not known. ‡For different fracture sites, actual numbers reported.

Table 5: **Occurrence of prespecified adverse events**

All three treatment regimens were well tolerated by most patients (table 7). Anastrozole was associated with significantly fewer withdrawals from treatment than tamoxifen (odds ratio 0·80 [0·71–0·90], p=0·0002), including significantly fewer withdrawals related to adverse events (0·68 [0·57–0·81], p<0·0001).

Discussion

Endocrine therapy for breast cancer has enjoyed a renaissance since the introduction of tamoxifen in the 1970s. Indeed, we can now be confident that, for hormone-receptor-positive patients, both premenopausal and postmenopausal, about 5 years of tamoxifen treatment is associated with a 47% reduction in disease recurrence rates and a 26% reduction in overall mortality.[5]

Although relatively well tolerated, about 30% of women on tamoxifen complain of hot flushes, vaginal discharge, or vaginal bleeding. Less common, although much more serious, are the long-term risks of endometrial cancer and

	Anastrozole (n=3092)	Tamoxifen (n=3094)	Combination (n=3097)	Total (n=9283)
Colorectal	24 (0·8%)	19 (0·6%)	9 (0·3%)	52 (0·6%)
Head and neck	5 (0·2%)	5 (0·2%)	5 (0·2%)	15 (0·2%)
Lung	8 (0·3%)	7 (0·2%)	4 (0·1%)	19 (0·2%)
Melanoma	0	6 (0·2%)	1 (0·0%)	7 (0·1%)
Ovary	6 (0·2%)	9 (0·3%)	6 (0·2%)	21 (0·2%)
Skin	39 (1·3%)	32 (1·0%)	27 (0·9%)	98 (1·1%)
Others	22 (0·7%)	28 (0·9%)	29 (0·9%)	79 (0·9%)
Total	104 (3·5%)	106 (3·4%)	81 (2·6%)	291 (3·2%)

Occurrences of contralateral breast cancers and endometrial cancers are not included in this table but are detailed in table 2 and table 5, respectively.

Table 6: **New primary cancers with an incidence of more than 0·2% before recurrence in all patients who received trial treatment**

	Anastrozole (n=3092)	Tamoxifen (n=3094)	Combination (n=3097)
All adverse events	2821 (91·2%)	2845 (92·0%)	2845 (91·9%)
Drug-related adverse events	1734 (56·1%)	1962 (63·4%)	1979 (63·9%)
Serious adverse events*	685 (22·2%)	755 (24·4%)	753 (24·3%)
Drug-related serious adverse events	83 (2·7%)	178 (5·8%)	152 (4·9%)
Overall withdrawal	676 (21·9%)	803 (26·0%)	819 (26·4%)
Withdrawal due to adverse events	241 (7·8%)	342 (11·1%)	337 (10·9%)
Withdrawals due to drug-related adverse events	159 (5·1%)	223 (7·2%)	228 (7·4%)

Patients can be included in more than one category. *Defined as those that were fatal, life-threatening, required hospital admission, caused disability or incapacity, or required medical intervention to prevent permanent impairment or damage.

Table 7: **Overall adverse events**

thromboembolic disease.[11,12,19] For these reasons, in addition to the potential for improved efficacy, we launched a trial of anastrozole, which lacks these partial agonist effects, in comparison with tamoxifen. A combination group was also chosen because of the theoretical possibility of additive or synergistic effects of two endocrine agents with different mechanisms of action.

The size of the ATAC trial, and the rapid rate of accrual, meant that the predetermined number of events needed to trigger the first formal analysis was achieved while patients had been on trial treatment for an average time of only half that stipulated in the protocol (ie, 2·5 years). About 43% of patients received 2–3 years of treatment, 30% received 3–4 years of therapy. Therefore, further follow-up will provide additional information on distant recurrence rates and survival.

In this first analysis, anastrozole showed better efficacy than tamoxifen (89·4% *vs* 87·4% disease-free survival rate at 3 years), with a 17% relative risk reduction in disease-free survival and a 19% improvement when compared with the combination group. For time to recurrence (breast-cancer events), larger differences in relative risk were seen (21% and 25% for anastrozole *vs* tamoxifen, respectively). The result was even greater in the subgroup known to be hormone-receptor-positive, in which the relative risk reduction in recurrence rates for anastrozole against tamoxifen increased to 27%. However, anastrozole was no more efficacious that tamoxifen in patients with hormone-receptor-negative disease.

An important point to note in relation to the efficacy analyses is the performance of tamoxifen in this trial. The tamoxifen event rate was almost identical to the 3·5% annual recurrence rate seen in the 1998 EBCTCG overview analyses when adjusted for nodal status.[5] Hence the benefits seen with anastrozole can be attributed to improved activity of the drug rather than to a suboptimum result with tamoxifen.

Combination treatment was equivalent to tamoxifen and significantly worse than anastrozole alone. Pharmacokinetic changes might explain the reduced efficacy of the combination. Although anastrozole concentrations were 27% lower in the combination group than in patients on anastrozole alone, the suppression of oestradiol concentrations was similar in the two groups,[20] indicating that this is unlikely to be the explanation. Administration of anastrozole with tamoxifen had no effect on tamoxifen concentrations or those of its major metabolites.

Pharmacological considerations might, however, provide one explanation for the greater efficacy of anastrozole than either tamoxifen or the combination. In the presence of postmenopausal oestrogen concentrations, tamoxifen saturates the oestrogen receptors and acts predominantly as an antagonist of oestrogen. But since tamoxifen is a partial agonist, it exerts some oestrogen-like signalling through the oestrogen receptor, which limits the degree of antagonism. By contrast, the profound oestrogen deprivation achieved by anastrozole alone might lead to near complete obliteration of oestrogen signalling and, therefore, greater efficacy than tamoxifen. Oestrogen-receptor binding of tamoxifen and its resultant minor oestrogenic signalling is likely to be unaffected by the withdrawal of oestradiol by anastrozole in the combination. Therefore the efficacy of tamoxifen and the combination would be equal. Other potential mechanistic explanations include the possible acquisition of different molecular resistance mechanisms for tamoxifen and anastrozole.

Compared with tamoxifen, anastrozole was associated with a 58% reduction in the incidence of contralateral cancers. Tamoxifen itself produced a significant reduction in this event compared with control when first reported in 1985.[5,21] This observation has been translated into a reduction in the incidence of breast cancer in women at high risk of the disease in the tamoxifen prevention trials which suggest an overall reduction of breast-cancer incidence of 38% (unpublished data). If this trend persists, anastrozole has the potential to prevent (or delay) up to 80% of hormone-receptor-positive breast cancers. As a consequence, anastrozole will be incorporated in the design of the second International Breast cancer Intervention Study (IBIS-II) prevention trial.[22]

An important consideration, especially in the adjuvant breast-cancer setting where drugs will be prescribed for long periods of time, is the side-effect profile of the drug. In the advanced breast-cancer setting, anastrozole has previously been associated with a significantly lower incidence of thromboembolic events than tamoxifen, and also fewer cases of vaginal bleeding.[15,16] Anastrozole has also been associated with slightly higher incidences of arthralgia and other joint disorders than tamoxifen.[23] The lower incidence of vaginal bleeding is postulated to be evidence for the lack of stimulatory effect of anastrozole on the endometrium.

The findings from the advanced-disease setting with respect to thromboembolic events, vaginal bleeding, and arthralgia were confirmed in this trial after long-term treatment. Among the predetermined adverse events analysed, in comparison with tamoxifen, treatment with anastrozole led to significantly fewer episodes of hot flushes, vaginal discharge, vaginal bleeding, endometrial cancer, strokes, and thromboembolic disease (including thrombophlebitis and deep venous thromboembolic events).

Although endometrial cancer is a rare event, its association with exposure to tamoxifen means that most women with tamoxifen-associated gynaecological symptoms are subjected to invasive and costly investigations. The reduction in the incidence of endometrial cancer among patients on anastrozole (to about the levels of endometrial cancer seen in a normal age-matched population) could, in the long term, save much unnecessary anxiety and health-care costs. These issues will be reported in greater detail later.

In the ATAC trial, women on anastrozole reported more musculoskeletal problems than those on tamoxifen. Prominent among these problems is a curious polyarthralgia, which seems to be a specific side-effect of this class of compound. Rheumatic symptoms have been reported to occur at an increased rate after treatment for

breast cancer,[24,25] after treatment with aromatase inhibitors,[23] post partum, and at menopause, suggesting a role of hormones in the development of rheumatic diseases.[26]

More serious is the significantly increased number of fractures seen in the anastrozole group. To some extent, this difference in fracture rate might be due to the protective effect of tamoxifen on bone compared with an untreated population; however, how much of this effect is also due to the additional effect of profound oestrogen suppression is unknown. This possibility is being investigated further in a subprotocol aimed at the prospective study of bone mineral metabolism in a sample population of the main ATAC trial. The extent to which bone problems can be ameliorated by treatment with bisphosphonates, which might also reduce the risk of skeletal metastases,[27] requires further investigation.

Two other consequences of chronic oestrogen deprivation need to be considered: the effects on lipid metabolism and cognitive function. The effect of aromatase inhibitors on lipid metabolism and, therefore, on the risk of ischaemic heart disease is not known. Data on anastrozole from the metastatic setting do not indicate any major effect on important lipid variables.[28] Longer-term follow-up of the ATAC trial is needed to provide the answers to this question. Results from other published studies provide conflicting data on the effect of HRT on cognitive function in healthy women. No comparative data are available, but this is an area of current research.

The findings for anastrozole in the ATAC trial are applicable only to newly diagnosed patients with early, operable breast cancer after initial treatment (surgery, radiotherapy, chemotherapy, or combinations thereof). The trial did not investigate the use of anastrozole in sequence after initiation of adjuvant treatment with tamoxifen treatment. These data cannot, therefore, be used to recommend that patients already being treated with tamoxifen should be switched to anastrozole. This question on sequencing is the subject of other ongoing clinical trials.

Evidence from this first analysis of the ATAC trial is encouraging, and these results could be as significant to breast cancer treatment as the results first seen with tamoxifen nearly 20 years ago. An important consideration at this time is how to treat newly diagnosed patients. An overall assessment of the benefits versus harm, based on current data, supports the use of anastrozole for the adjuvant treatment of early breast cancer in postmenopausal women, meaning that there is now a choice of adjuvant endocrine therapy for postmenopausal women with hormone-responsive tumours.

Conflict of interest statement

M Baum, J Cuzick, J Houghton, A Buzdar, J Forbes, J S Tobias, and J Klijn have all received travel awards and honoraria from AstraZeneca for the purposes of attending the ATAC trial steering committee meetings or presenting the ATAC trial results. M Baum has been an independent paid consultant for AstraZeneca. J Houghton holds a contract with AstraZeneca for operational management and to support some of the monitoring of the trial. J Cuzick is a principal investigator of an unrestricted educational grant awarded to Cancer Research UK from AstraZeneca to evaluate aromatase inhibitors in breast cancer prevention, and is also an independent statistical consultant to AstraZeneca. T Sahmoud is an employee of AstraZeneca.

The ATAC Trialists' Group

Writing Committee—M Baum (Chairman and Principal Investigator for the main ATAC trial), A U Buzdar, J Cuzick (Independent Statistician), J Forbes, J Houghton, J G M Klijn, T Sahmoud.
Steering Committee Membership—M Baum, A R Bianco, A U Buzdar, M Coibion, J Cuzick, M Dowsett, W D George, J Gray, J Houghton, N Williams, A Howell, T Sahmoud, R Hellmund, L Thornton, J S Tobias.
International Coordinating Committee—A R Bianco, A U Buzdar, M Coibion, M Constenla, W Distler, J Forbes, A Howell, W D George, J P Guastalla, J G M Klijn, G Y Locker, R E Mansel, J M Nabholtz, T Nagykalnai, A Nicolucci, U Nylen, T Sahmoud, R Sainsbury.
International Project Team—E Foster, N Griffiths, J Houghton, N Williams, A Nicolucci, S Pollard, T Sahmoud.
Independent Data Monitoring Committee—M Buyse, R Margolese, J M A Northover.
Collaborative/Operational Groups—Australian New Zealand Breast Cancer Trials Group Operations Office: J F Forbes, J K Wakeham. Universita degli Studi Di Napoli Federico II, Italy: S de Placido, C Carlomagno. GIVIO Group, Consorzio Mario Negri Sud, Italy: A Nicolucci, M Belfiglio, M Valentini. Scottish Cancer Therapy Network (SCTN), Information & Statistics Division, Edinburgh, UK: L Foster. Northern & Yorkshire Clinical Trials Research Unit (NYCTRU), University of Leeds, Leeds, UK: S Pollard. Cancer Research UK & UCL Cancer Trials Centre, London, UK: J Houghton, N Williams.

Principal and main co-investigators in ATAC Trial

Argentina—F Coppola, C Bas, J Itala, G Cortese, A Nuñez de Pierro, D Allemand, R Orti, R Testa, J Lebron.
Australia—G Gill, J Kollias, J Chirgwin, M Leyden, J Beith, A Sullivan, S Della-Fiorentina, A Goldrick, G Richardson, S Hart, G Toner, P Francis, R Snyder, I Burns, M Friedlander, D Goldstein, J Forbes, D Jackson.
Belgium—A Makar, D Van den Weyngaert, D Gangji, T Velu, M Coibion, J-M Nogaret, P Neven, C Laurent, J De Mol, F Van Aelst.
Canada—S R Sehdev, R Simard, J R MacKey (J-M Nabholtz former PI), J Dufresne, W S Lofters, D R Holland, H L Solow, J A Gapski, S H Rubin (O R Keller former PI), A Robidoux, B Lesperance, L C Panasci, L A Zibdawi, J Chang, M L Brigden (D L Saltman former PI), R F Wierzbicki, B P Findlay, J Robert, S Lebel (M Potvin former PI), M R B T Tirona, M J Burnell, O R Keller (B A Walley former PI), P L D Walde, S-C Tang, C J Germond, Y Rahim, J J Wilson, A L Cooke (D M Bowman former PI).
Czech Republic—K Petrakova, R Demlova, P Vodvarka, T Kysela, B Konopasek, P Mares.
France—J-Edouard Mention, D Serin, Y Goubely-Brewer, J-P Labat, J-P Malhaire, G Devulder, S Mirdat-Dako, D Houze De L'Aunoit, J-Y Charvolin, J-P Guastalla, T Bachelot, R Coquard, B Velay, C Lejeune, D Hadjadj-Aoul, M Untereiner, O Rixe, F Laffargue, M Rios, J-M Vannetzel, R Mahjoubi, R Samak, F Morvan, F Rousseau, C Veyret, J P Julien, B Cutuli, P Quetin, J-P Brettes, C Mathelin.
Germany—W Distler, A Schindelhauer, W Jaeger, G Wieland, C Oberhoff, D Hanisch, J Bechler, S Malur, W Eiermann, G Raab.
Hungary—C Polgar, K Moskovits, Z Nagy, T Nagykalnai, L Landherr, T Pinter, G Herodek, B Piko, I Szegedi, J Szanto, L Marazi, Z Kahan.
Ireland—E McDermott, N O'Higgins, T Gorey, F Given, S Tormey.
Italy—M Bonsignori, S Rossini, F Di Vito, M Cucchi, F Testore, L Giaretto, F Recchia, S De Filippis, M De Lena, F Schittulli, A Martoni, E Piana, G Marini, P Marpicati, M Pintus, A Tedde, M Botta, D Degiovanni, L Basilico, M Taraborrelli, S Bravi, F Biagioni, M Giordano, G Luchena, G Scognamiglio, A Beretta, P Marchetti, ME D'Addario, M Obialero, F Peradotto, M Indelli, G Lelli, A Nuzzo, L Laudadio, M D'Aprile, M Natali, G Cruciani, E Montanari, E Aitini, G Cavazzini, V Adamo, G Altavilla, S Barni, A Ardizzoia, A De Matteis, G Landi, G D'Aiuto, R Thomas, R Lauria, M De Laurentis, A Fornasiero, H Koussis, G Brignone, L Mesi, A Riccardi, P Pugliese, G Pavia, T Porro, F Cognetti, P Papaldo, G Gasparini, M A Castellana, M Mattarei, S Robbiati, A Farris, G Sanna, C Vucusa, M Viglietta, G Fornari, A Turletti, E Arnoldi, A Richetti, M Molteni.
New Zealand—I Campbell, R Gannaway.
Poland—J Tujakowski, M Osmanska, P Koralewski, M Urbanska, B Karczmarek-Borowska, B Kukielka-Budny, M Teresiak, P Laski, M Krzakowski, E Pucula.
Portugal—A Alcazar, O Campos, I Botto, O Candeias, H Ramires, M Chumbo, H Gervasio, D Jardim da Pena, R Nabiço, C Oliveira, E Abraul.
Slovak Republic—S Spanik, I Vochyanova, M Wagnerova, I Andrasina.
South Africa—A Maxwell, L Goedhals, L Smith, I Werner, E Murray, J Apffelstaedt, I Loubser, D Hacking, G Landers, D Vorobiof.
Spain—A Barnadas, C Alonso Muñoz, J Baselga, J Tabernero, M Beltrán, E Canals, S Menjón, L Calvo, J R Mel, G Quintero, G Perez Manga, A Alonso, P España, R Cubedo Cervera, C Sánchez Martínez, M Repolles Escarda, P Aramburo, J E Alés, J J Valerdi, M Tejedor Gutierrez, M Constenla, R Garcia Arroyo, J Lizon, C Angeles, J M Lopez-Vega, D Menedez, J A Moreno Nogueira, P Borrego, J Montalar, A Santaballa, V Guillem, A Llombart, G Huidobro Vence, J Casal.
Sweden—S-Å Olsson, L Ryden, S Rotstein, D Pettersson-Sköld, B Börjesson, P-E Jönsson, M Malmberg, L Lovén, I Grybäck, C Ingvar, P Lindblom, S B Holmberg, U Nylén, E Lidbrink, T Fornander, G Winblad, R Fernstad, L Löfgren, T Ambré, M Nilsson.
The Netherlands—L Siegenbeek van Heukelom, R Boom, D van Geldere, A de Boer, E Maartense, D Halkema, C Dijkhuis, M van Hennik, P Willemse, H van Veelen, H de Graaf, E Bruggink, L Strobbe,

D de Gooyer, J Janssen, M Leijs, J Stouthard, J Klijn, C Seynaeve, F Erdkamp, F Kauw, A van Reisen, C van der Heul, J Ruit, L Kerhofs, R de Kan, R Hellingman, E Trommel, J Coenen.
Turkey—E Baltali, A Aydiner.
UK—A Hutcheon, T Sarkar, T Bates, N Griffiths, M Carr, C Alcock, B Lavery, E Sugden, N Stuart, D Crawford, A Wilkinson, G Odling-Smee, W Abram, A Patterson, A Aukland, D Spooner, H Bishop, R Salem, T Hickish, A Skene, C Bradley, D Parker, S Cawthorn, M Shere, S Goodman, E Whipp, A Moody, C Wilson, E Cox, R Mansel, H Sweetland, P Sauven, S Chandrasekharan, G Layer, P Murray, F MacNeill, J Fox, A Ball, G Rawsthorne, R Blunt, J Dewar, A Thompson, W Taylor, A Cook, I Kunkler, D Cameron, R Leonard, W Cunliffe, D Browell, W D George, A N Harnett, C T Twelves, D C Smith, M Kissin, V Modgill, P Surtees, R Knox, J Joffe, B Lavery, A Harris, J Nicholls, S Raymond, N Rowell, J LeVay, T Archer, A Nejim, I Hutchinson, M Lansdown, T Perren, K Horgan, D Dodwell, C Holcombe, J Rainey, G Howard, S Holt, Y Sharaiha, J Tobias, M Gaze, J Mansi, N Sacks, C Coulter, S Stewart, A Jones, T Davidson, J R C Sainsbury, A Wilson, I Smith, G Gui, D Matheson, A Howell, A Stewart, L Barr, N Bundred, P Durning, A Clason, A Mitchell, R Souter, C Griffith, A Griffiths, C Gaffney, M Stokes, J Dawson, S Powis, I Goulbourne, A Makris, E Maher, J R Robertson, R Blamey, R Nangalia, H Bishop, I McIntosh, D Pinto, A Jones, R Watkins, S Prance, C Tyrrell, P Macleod, C Yiangou, P Perry, C Humphrey, M Quigley, Z Saad, E Hoare, R Coleman, S Kohlhardt, B Harrison, R Agrawal, P Forouhi, P Canney, P England, C Hennessy, A Peel, E Hoare, S Kelly, K Stepp, D Sebag-Montefiore, R Grieve, T Waterworth, G Copeland, D Jones, A Robinson, C Trask, P Barrett-Lee, R Rainsbury, V Hall, D Berstock, R Errington, D Fairlamb, A Salman, A Johri, S Goodman, G Sparrow, S Nicholson.
USA—A Mangalik, S J Yee, K Tkaczuk, M Thant, C E Hartz, G P Miletello, W J Popovic, D B Myers, M R Thomas, A J Koletsky, E G Levine, C F White, G Grana, K E Weeman, L L Schlabach, S G Taylor, P Silverman, D L Headley, M F Gonzalez, L R Laufman, JL Blum, H S Shaw (L N Harris former PI), N Dimitrov (D MacDonald former PI), E T O'Brien, G Y Locker, N J Robert, M S Rubin, G R Justice, T J O'Rourke (J R Borst former PI); A U Buzdar, J K Hon, R H Clark, H B Sher, K B Pendergrass, AM Grossman, HP DeGreen, R Kosierowski, H J Allen, J D Conroy (M A Simmonds former PI), J J Sternberg, L Bhupalam (G C Michelson former PI), M H Ward, P T Silberstein, P V Pickens, M A Schwartz, J Singson, J G Schneider, M M Oken, MW Meshad, F A Greco, M J Guarino, K K Boatman, J A Mailliard, A S Kelley, D W Northfelt (E S Camacho former PI), R A Hirsch, B R Piccone, M S Roberts, J I Spector, N Tirumali (A G Glass former PI), M A Deutsch, D M Sahasrabudhe, P Bushunow (M Brower former PI), T J Woodlock (K J Pandya former PI), W R Edwards, I A Jaiyesimi, F C Kass, L W Keiser, G V Burton, J C Michalak, M S McHale, J R Goodman, P D Byeff, K L Hoelzer, E P Lester, A P Lyss, M E Woodson, H S Puc, F Senecal, J Horton, R R Young, I S Lowenthal, H B Nevinny, E P Gelman (D F Hayes former PI) (M J C Ellis former PI), M A Vukelich, K Seetharaman (L L Stolbach former PI).

A full list of investigators can be found at http://image.thelancet.com/extras/02art5373appendix.pdf

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