Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial

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Summary

Background **Early improvements in disease-free survival have been noted when an aromatase inhibitor is given either instead of or sequentially after tamoxifen in postmenopausal women with oestrogen-receptor-positive early breast cancer. However, little information exists on the long-term effects of aromatase inhibitors after treatment, and whether these early improvements lead to real gains in survival.**

Methods **4724 postmenopausal patients with unilateral invasive, oestrogen-receptor-positive or oestrogen-receptor-unknown breast cancer who were disease-free on 2–3 years of tamoxifen, were randomly assigned to switch to exemestane (n=2352) or to continue tamoxifen (n=2372) for the remainder of a 5-year endocrine treatment period. The primary endpoint was disease-free survival; overall survival was a secondary endpoint. Efficacy analyses were intention-to-treat. This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN11883920.**

Results **After a median follow-up of 55·7 months (range 0–89·7), 809 events contributing to the analysis of disease-free survival had been reported (354 exemestane, 455 tamoxifen); unadjusted hazard ratio 0·76 (95% CI 0·66–0·88, p=0·0001) in favour of exemestane, absolute benefit 3·3% (95% CI 1·6–4·9) by end of treatment (ie, 2·5 years after randomisation). 222 deaths occurred in the exemestane group compared with 261 deaths in the tamoxifen group; unadjusted hazard ratio 0·85 (95% CI 0·71–1·02, p=0·08), 0·83 (0·69–1·00, p=0·05) when 122 patients with oestrogen-receptor-negative disease were excluded.**

Conclusions **Our results suggest that early improvements in disease-free survival noted in patients who switch to exemestane after 2–3 years on tamoxifen persist after treatment, and translate into a modest improvement in overall survival.**

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Introduction

For many years tamoxifen was recognised as the standard adjuvant endocrine treatment for oestrogen-receptor-positive breast cancer. In women with oestrogen-receptor-positive (or oestrogen-receptor-unknown) disease, 5 years of treatment with tamoxifen after definitive surgery was shown to reduce the annual recurrence rate by 41% and breast cancer mortality by 34%, translating into an absolute reduction of 9·2% in patients dying from breast cancer by 15 years.[1] In addition to benefit noted while patients are on treatment, further gain is seen during the 5 years after treatment.

Aromatase is the key enzyme responsible for oestrogen biosynthesis; aromatase inhibitors have been in use for three decades. Third-generation aromatase inhibitors (letrozole, anastrozole, and exemestane) are effective in postmenopausal patients with hormone-sensitive advanced breast cancer resistant to tamoxifen.[2–5] Large randomised trials have reported early improvements in disease-free survival during treatment with an aromatase inhibitor compared with tamoxifen in the adjuvant setting. Clinical applications have included upfront monotherapy with an aromatase inhibitor,[6,7] a switch to an aromatase inhibitor after 2–3 years of tamoxifen,[8–10] and a comparison with placebo in the extended adjuvant setting.[11,12] Importantly, this benefit is accompanied by a reduction in the commonly recognised side-effects of tamoxifen. However, concern has been raised about the effects of aromatase inhibitors on other aspects of safety, including effects on bone loss and the cardiovascular system.

The Intergroup Exemestane Study (IES) was designed to ascertain whether switching to exemestane, a steroidal aromatase inhibitor, after 2–3 years of tamoxifen could improve disease outcome compared with continuing tamoxifen for the remainder of the 5-year treatment period. We postulated that use of both treatments in sequence would improve efficacy and reduce side-effects compared with use of either treatment alone, since carry-over from early exposure to tamoxifen would provide continuing disease-related benefits and, through its oestrogenic effects, ameliorate some of the adverse effects of aromatase inhibitors, such as excess calcium loss. Further, we reasoned that switching might reduce the tamoxifen-associated incidence of thromboembolism and endometrial cancer.

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Early release of the results of IES, on the recommendation of the Independent Data Monitoring Committee (IDMC), was prompted by a significant early improvement in disease-free survival, which exceeded the predefined statistical stopping boundary.[8] At the time of publication more than 90% of patients had completed allocated treatment, so that dissemination of results was unlikely to contaminate the trial.[13] With a median follow-up of 30·6 months, 449 disease-free survival events, and 199 deaths, switching to exemestane reduced the risk of events contributing to the analysis of disease-free survival by 32% but at this early time point, overall survival did not differ between the treatment groups.

In this analysis, with a median follow-up of almost 5 years and more than 10 000 women-years of post-treatment information, we investigated whether early disease-related benefits persisted after treatment and whether any long-term adverse risks had emerged.

Methods

Study design

IES was an international, intercooperative group, phase III trial in postmenopausal women previously diagnosed with oestrogen-receptor-positive or oestrogen-receptor-unknown breast cancer who received adequate local and adjuvant systemic treatments including tamoxifen (and chemotherapy if indicated). Women who remained free of disease on tamoxifen after 2–3 years were randomised to switch to exemestane (25 mg daily) or to continue tamoxifen (20 mg or 30 mg [Denmark] per day) for the remainder of the 5-year endocrine treatment period. The study design, eligibility criteria, treatment schedules, and statistical analysis plan have been previously described.[8]

Site monitoring was done by representatives of Pfizer or by the co-operative groups. All data was sent to the coordinating data centre where it was entered centrally onto the clinical database. All statistical analyses were done within the coordinating data centre. Adverse events were graded according to Common Toxicity Criteria grades (December, 1994, revised version) and coded using the Medical Dictionary for Regulatory Activities (MedDRA version 5.1). Serious cardiovascular events were reviewed by an independent cardiologist who also defined higher level cardiovascular groupings to facilitate comparison with other studies. All second primary cancers were reviewed to ascertain any potential confusion with metastatic breast cancer. For such cases, histological and where relevant, radiological reports underwent a double central review by investigators (RCC and ASC) blind to allocated treatment. This analysis includes all data processed by the coordinating data centre by Feb 27, 2006.

Statistical analysis

After publication of IES, advice was sought from the trial's IDMC and steering committee to define the criteria required to trigger an updated analysis. The following procedure was agreed: to undertake an updated analysis when 95% of patients had had at least 3 years follow-up or had died during the corresponding period, and to do a supplementary analysis (in addition to the protocol-defined

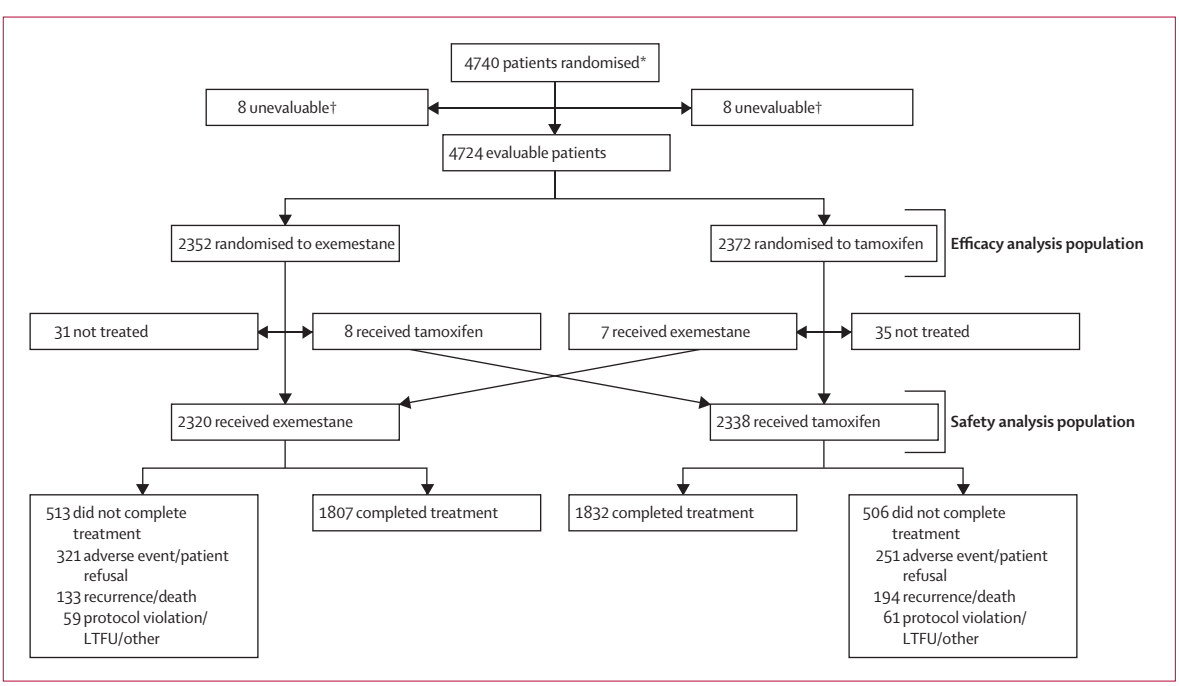


Figure 1: **Trial profile**

LTFU=lost to follow-up. *2 patients with duplicate patient identifiers were identified, thus the total number of patients randomised is 2 fewer than previously reported.[8] †Monitoring for regulatory submission has resulted in an inability to confirm the validity of data at one individual centre. On that basis, it was agreed that no data from patients entered at that centre (n=16) be used in further analyses.

intention-to-treat [ITT] analysis), excluding patients subsequently found to have had oestrogen-receptor-negative disease.

The primary endpoint was disease-free survival, with events contributing to the analysis defined as local and distant breast cancer recurrence, new primary breast cancer (ipsilateral or contralateral) and death without disease relapse (intercurrent death). Secondary endpoints included overall survival and incidence of contralateral breast cancer. For comparison with other studies, breast-cancer-free survival (censoring intercurrent deaths of known cause) and time to distant recurrence (distant recurrence, deaths from breast cancer, deaths with unknown cause with no metastases reported) were also analysed. Breast cancer deaths constituted all those with confirmed cause of breast cancer, cause unknown or death from any cause following a breast cancer relapse.

We analysed survival endpoints using log-rank tests, Kaplan Meier plots, Nelson Aalen cumulative hazard plots, and Cox proportional hazards models with and without adjusting for pre-specified prognostic factors of oestrogen-receptor status, nodal status, use of chemotherapy, and use of hormone replacement therapy. The proportionality assumption of the Cox model was tested with Schoenfeld residuals and was found to hold. Absolute differences in survival at 2·5 years after randomisation (roughly equivalent to 5 years post-diagnosis and coinciding with end of treatment for most patients) and at 5 years after randomisation are also reported.[14] All efficacy analyses were ITT and the pre-defined oestrogen-receptor-positive or oestrogen-receptor-unknown groups. Additional analyses were done with the survival times divided into the periods on-treatment (0–2·5 years) and post-treatment (2·5 years onwards). The criterion for statistical significance for efficacy analyses was set at $\alpha=0{\cdot}05$ (two-sided). No adjustment was made for multiple testing in these analyses.

Analyses of adverse events were done according to actual treatment received and worst adverse event grade reported after randomisation. A sensitivity analysis using the intention-to-treat group produced results very similar to those reported (data not shown). On-treatment analysis included adverse events occurring between randomisation and 30 days after last study treatment, censoring patients at time of relapse or second primary cancer. A second safety analysis extended the at-risk time period, including both on-treatment and post-treatment adverse events (again censoring at relapse or second primary cancer). For all safety analyses the criterion for statistical significance was set at $\alpha=0{\cdot}01$ because of the large number of statistical tests (with corresponding 99% CIs presented). Adverse events have been presented in two complementary formats: all MedDRA coded adverse events satisfying predefined criteria (ie, ≥10% incidence, $p<0{\cdot}01$ or >1% difference in incidence between treatment arms); and graphical illustration of the odds ratio (OR) of adverse events types known to be of clinical interest in the study of endocrine therapy in breast cancer patients (ie, gynaecological, musculoskeletal, and cardiovascular events) irrespective of

	Exemestane (n=2352)	Tamoxifen (n=2372)	Total (n=4724)
Age group (years)			
<60	763 (32·4%)	760 (32·0%)	1523 (32·2%)
60–69	1005 (42·7%)	1016 (42·8%)	2021 (42·8%)
≥70	584 (24·8%)	596 (25·1%)	1180 (25·0%)
Nodal status			
Negative	1217 (51·7%)	1230 (51·9%)	2447 (51·8%)
1–3 N+	722 (30·7%)	709 (29·9%)	1431 (30·3%)
≥4 N+	328 (13·9%)	330 (13·9%)	658 (13·9%)
Missing/unknown	85 (3·6%)	103 (4·3%)	188 (4·0%)
Previous chemotherapy use			
Yes	774 (32·9%)	768 (32·4%)	1542 (32·6%)
No	1578 (67·1%)	1604 (67·6%)	3182 (67·4%)
Hormone-receptor status			
ER+ and PgR+	1340 (57·0%)	1328 (56·0%)	2668 (56·5%)
ER+ and PgR–/unknown	681 (29·1%)	693 (29·2%)	1374 (29·1%)
ER unknown and PgR+/unknown	275 (11·7%)	285 (12·0%)	560 (11·9%)
ER– and PgR+	6 (0·3%)	8 (0·3%)	14 (0·3%)
ER– and PgR– /unknown	50 (2·1%)	58 (2·5%)	108 (2·3%)
Histological type			
Infiltrating lobular	341 (14·5%)	321 (13·5%)	662 (14·0%)
Infiltrating ductal	1777 (75·6%)	1830 (77·2%)	3607 (76·4%)
Other	231 (9·8%)	214 (9·0%)	445 (9·4%)
Unknown/missing	3 (0·1%)	7 (0·3%)	10 (0·2%)
Type of surgery			
Mastectomy	1204 (51·2%)	1222 (51·5%)	2426 (51·4%)
Wide local excision	886 (37·7%)	922 (38·9%)	1808 (38·3%)
Other	259 (11·0%)	223 (9·4%)	482 (10·2%)
Unknown/missing	3 (0·1%)	5 (0·2%)	8 (0·2%)
Previous HRT use			
Yes	565 (24·0%)	559 (23·6%)	1124 (23·8%)
No	1731 (73·6%)	1756 (74·0%)	3487 (73·8%)
Unknown/missing	56 (2·4%)	57 (2·4%)	113 (2·4%)
Tumour size			
<2 cm	1148 (48·8%)	1105 (46·6%)	2253 (47·7%)
2–5 cm	1088 (46·3%)	1160 (48·9%)	2248 (47·6%)
>5 cm	63 (2·7%)	59 (2·5%)	122 (2·6%)
Missing	53 (2·3%)	48 (2·0%)	101 (2·1%)
Tumour grade			
G1	397 (16·9%)	393 (16·6%)	790 (16·7%)
G2	977 (41·5%)	1009 (42·5%)	1986 (42·0%)
G3	454 (19·3%)	427 (18·0%)	881 (18·6%)
Undifferentiated	23 (1·0%)	19 (0·8%)	42 (0·9%)
Not assessable	56 (2·4%)	47 (2·0%)	103 (2·2%)
Missing /unknown/not assessed	445 (18·9%)	477 (20·1%)	922 (19·5%)
Duration of previous tamoxifen treatment (months)			
Mean (SD)	29·2 (4·1)	29·2 (4·2)	29·2 (4·2)

Data are number (%) unless otherwise specified. ER=oestrogen-receptor. PgR=progesterone receptor. +=positive. –=negative. N=node. HRT=hormone replacement therapy.

Table 1: **Baseline demographics and characteristics**

	Exemestane	Tamoxifen	Total
Total DFS events	354	455	809
Local recurrence	49	68	117
Distant recurrence	216	257	473
Contralateral breast cancer	18	35	53
Other death*	71	95	166
Total deaths	222	261	483
Breast cancer deaths	151	166	317
Intercurrent deaths	71	95	166
Cause of death known	63	80	143
Other cancer	18	35	53
Vascular	17	11	28
Cardiac	14	13	27
Other	14	21	35
Cause of death unknown*	8	15	23

*Deaths of unknown cause were treated conservatively as breast cancer deaths in the efficacy analysis.

Table 2: **Events by treatment group (ITT)**

statistical significance or incidence. χ^2 tests, including tests for trend, were used as appropriate. Fracture incidence per 1000 women-years, incorporating multiple distinct fracture occurences per patient, was calculated. All analyses were done with Stata version 9.1.

This study is registered as an International Standard Randomised Controlled Trial, number ISRCTN11883920.

Role of the funding source

The study was developed by the steering committee of the International Collaborative Cancer Group, with additional input from representatives of other collaborative groups. The sponsor had limited input in the study design, provided funding, and gave organisational and monitoring support to the coordinating data centre where the database was held independently. Transfers of frozen copies of the database were provided to the sponsor for submission to the regulatory authorities and fulfilment of regulatory responsibilities. All members of the steering committee, including sponsor representatives, were given the

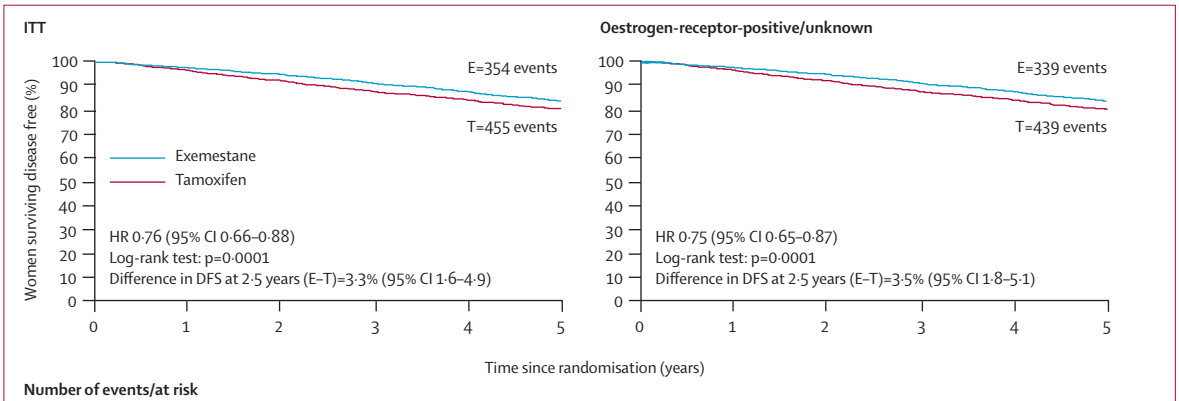


Figure 2: **Kaplan Meier plots for disease-free survival (DFS)**
E=exemestane. T=tamoxifen.

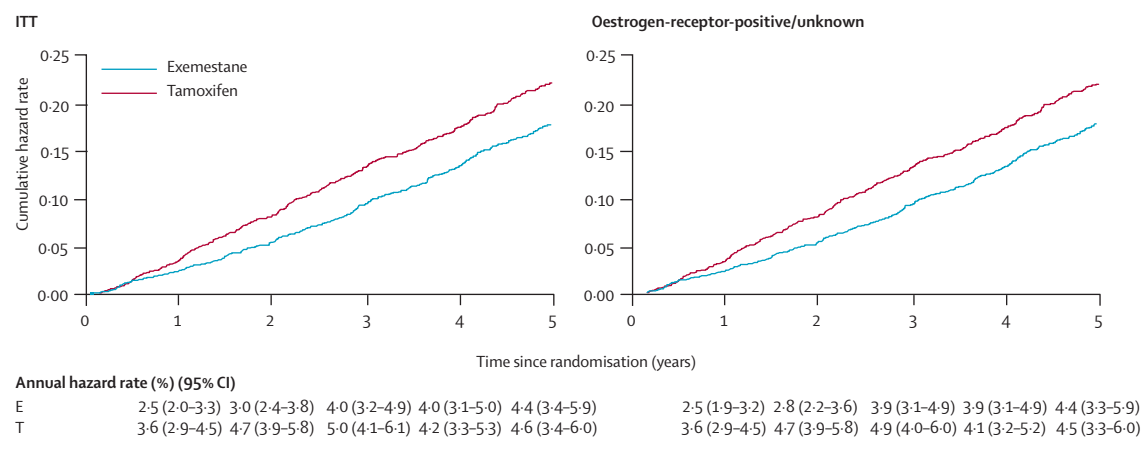


Figure 3: **Nelson Aalen cumulative hazard plots for disease-free survival**
E=exemestane. T=tamoxifen.

opportunity to critically review the manuscript; however editorial control was retained by the members of the steering committee independent of the sponsor. The sponsor was represented in a minority on the trial's steering committee. All analyses were done by the coordinating data centre in agreement with the trial's IDMC and steering committee. The corresponding author had access to all study data and took final responsibility for the decision to submit for publication.

Results

4724 patients with evaluable data were randomised from 37 countries and 366 sites between 1998 and 2003. With a median follow-up of 55·7 months (range 0–89·7) the present analysis provides 10456 women-years of on-treatment data (5162 exemestane and 5294 tamoxifen) and 10335 women-years of post-treatment follow-up. More than 95% of patients had at least 3 years of follow-up or had died during the corresponding period. Figure 1 shows the trial profile and table 1 shows patients' characteristics. Since randomisation, previously unknown oestrogen status has been ascertained in 381 patients. 122 patients were identified as having had oestrogen-negative tumours.

Table 2 shows the numbers of patients with disease-free survival events and numbers of deaths. Of the 809 disease-free survival events so far reported, 354 were in patients allocated to switch to exemestane and 455 in patients allocated to remain on tamoxifen. Overall in the ITT group, the unadjusted hazard ratio (HR) for disease-free survival was 0·76 (95% CI 0·66–0·88; p=0·0001) in favour of exemestane (figure 2). In the oestrogen-receptor-positive and oestrogen-receptor-unknown group, very similar results were obtained, with a HR of 0·75 (95% CI 0·65–0·87; p=0·0001). In the ITT group, this HR translated into a 3·3% (95% CI 1·6–4·9) absolute improvement in disease-free survival at 2·5 years after randomisation, and a 3·4% (0·1–6·8) improvement 5 years after randomisation. For the oestrogen-receptor-positive and oestrogen-receptor-unknown group, the absolute improvement at 2·5 years was 3·5% (95% CI 1·8–5·1) and at 5 years was 3·5% (0·1–6·9). Figure 3 shows a lower annual hazard rate during the on-treatment period in patients who switch to exemestane than in those who stay on tamoxifen; early divergence of the cumulative hazard rates was maintained throughout the post-treatment period. By partitioning the survival time, a HR of 0·65 (95% CI 0·53–0·80) was noted for the on-treatment (0–2·5 years) period, with potential further gain, but no material loss seen post-treatment (HR 0·86; 95% CI 0·71–1·05). Adjusting for potential confounders did not substantially affect the estimates of treatment effect, and the size of benefit for switching to exemestane seemed consistent across subgroups (figure 4). Breast-cancer-free survival, time to distant recurrence, and time to contralateral breast cancer were all improved by switching to exemestane (table 3) for the ITT group and the oestrogen-receptor-positive or oestrogen-receptor-unknown group.

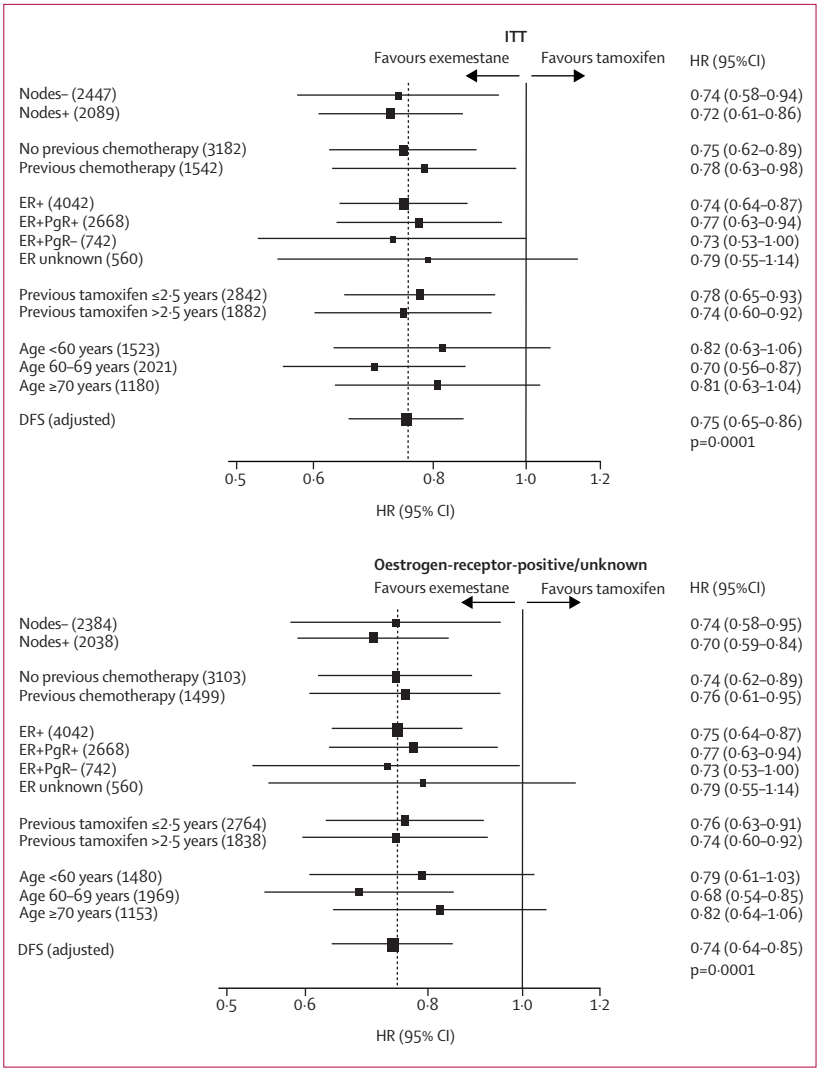


Figure 4: **Subgroup analysis forest plot for disease-free survival (DFS)**
+=positive. –=negative. ER=oestrogen-receptor. PgR=progesterone-receptor. Forest plots display subgroup analyses depicting the HR as the centre of the box and 95% CI as a horizontal line, the box size being proportional to the precision of the estimate.

At a median follow-up time of almost 5 years, about 10% of patients had died (table 2). Of the 483 deaths reported, 222 occurred in patients allocated exemestane and 261 in those allocated tamoxifen. 317 deaths had known breast-cancer cause or followed a breast-cancer relapse (151 exemestane, 166 tamoxifen), with an additional

	ITT group		Oestrogen-receptor-positive/unknown group	
	HR (95% CI)	p	HR (95% CI)	p
Breast-cancer-free survival	0·76 (0·65–0·89)	0·0004	0·75 (0·64–0·88)	0·0003
Time to distant recurrence	0·83 (0·71–0·99)	0·03	0·83 (0·70–0·98)	0·03
Time to contralateral breast cancer	0·57 (0·33–0·98)	0·04	0·56 (0·33–0·98)	0·04

Table 3: **HR (95% CI) for other efficacy endpoints (exemestane *vs* tamoxifen group)**

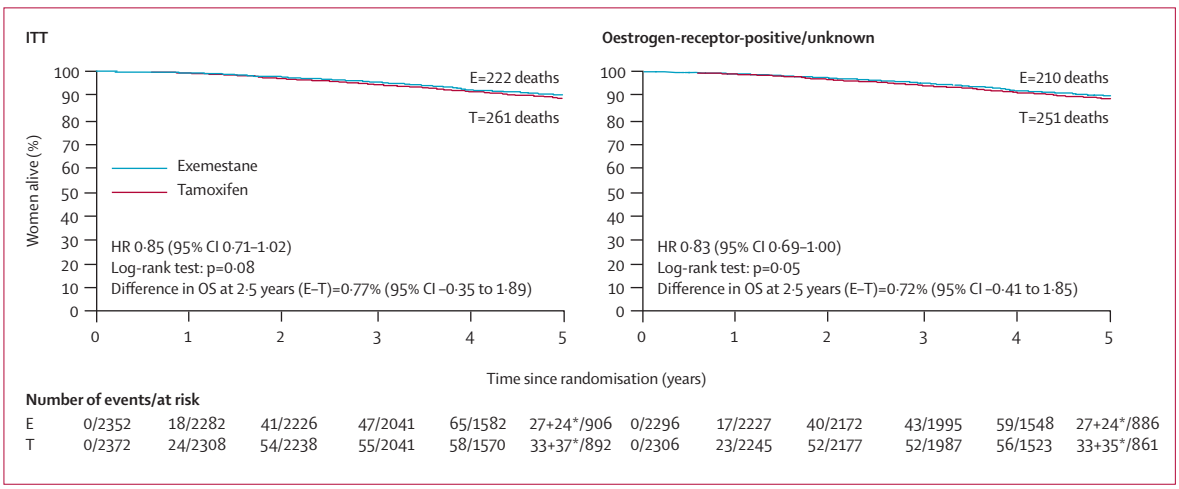


Figure 5: **Kaplan Meier plots for overall survival (OS)**
E=exemestane. T=tamoxifen.

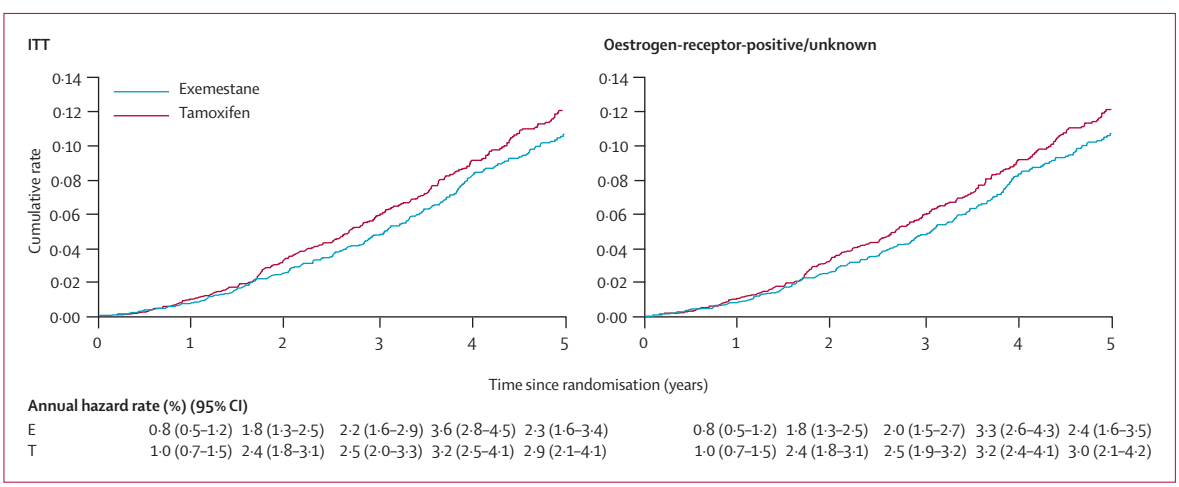


Figure 6: **Cumulative hazard plots for overall survival**
E=exemestane. T=tamoxifen.

23 patients (eight exemestane, 15 tamoxifen) dying of unknown cause and considered likely to be deaths due to breast cancer. Fewer deaths due to cancers other than breast cancer occurred in the exemestane group than in the tamoxifen group. Numbers of deaths due to vascular and cardiac causes were infrequent in both treatment groups. In the ITT analysis, 222 deaths occurred in the exemestane group and 261 in the tamoxifen group (15% relative reduction in risk of death, 95% CI consistent with 29% reduction to 2% increase, p=0·08; figures 5 and 6). When 122 patients with oestrogen-receptor-negative disease were excluded, 210 patients died in the exemestane group compared with 251 in the tamoxifen group (17% relative reduction, 95% CI consistent with 31% reduction to no change, p=0·05; figures 5 and 6). The divergence between curves emerged within 2 years and persisted throughout the post-treatment period. Again, benefit was consistent across subgroups, although precision was limited by the relatively small numbers of events (figure 7). Adjusting for potential confounders gave results very similar to the unadjusted results (ITT analysis: HR 0·85, 95% CI 0·71–1·01); p=0·07; oestrogen-receptor-positive and oestrogen-receptor-unknown group: 0·83, 0·69–0·99; p=0·04).

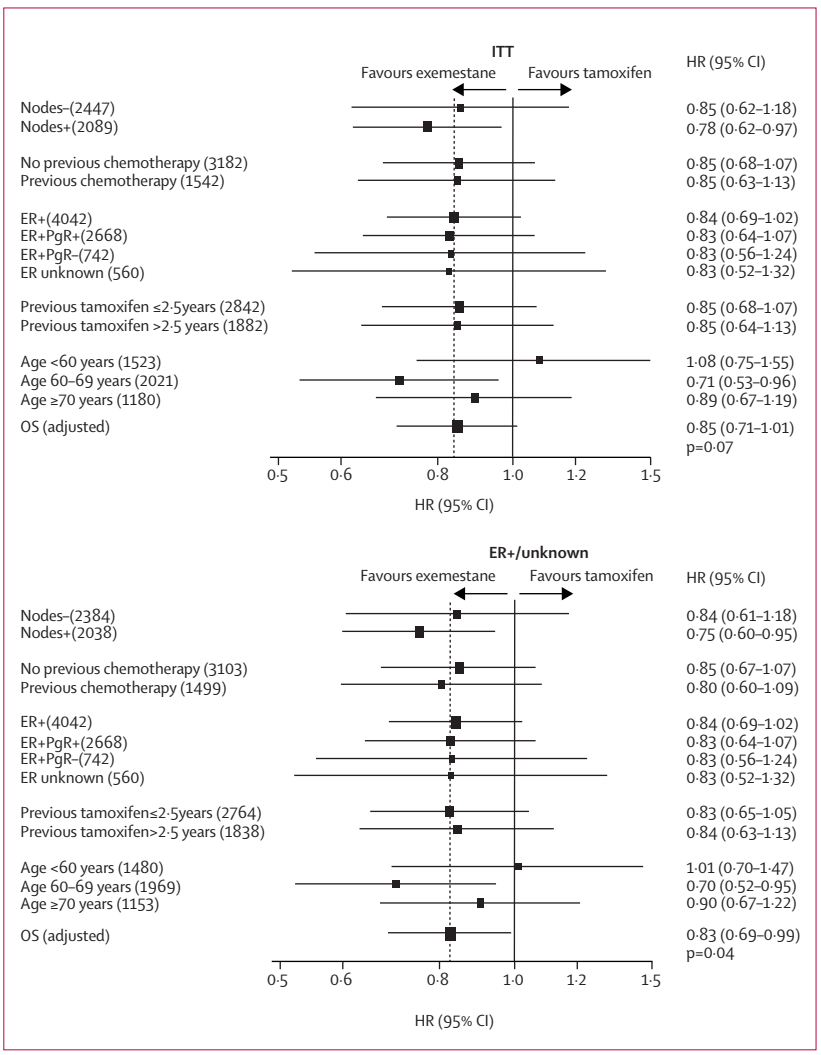
4658 (99·6%) patients received some study treatment; 2146 (92.5%) of those taking exemestane reported an adverse event of any grade, compared with 2165 (92·6%) on tamoxifen. Grade 3 or 4 adverse events were noted in 426 (18·4%) patients on exemestane and 411 (17·6%) on tamoxifen. Table 4 shows the on-treatment safety analysis and table 5 includes adverse events that occurred during treatment and post-treatment. Forest plots showing symptoms of most clinical interest are shown in figure 8.

Patients who received exemestane reported fewer venous thromboembolic events on treatment than did those on tamoxifen (table 4). The incidence of cardiovascular events (excluding venous thromboembolic events) did not seem to differ between the groups while on treatment or when

post-treatment events were included (tables 4 and 5). No other statistically significant differences in reported cardiovascular events were noted either on-treatment or including the post-treatment period. Myocardial infarctions were rare and occurred in 31 (1·3%) exemestane-treated patients compared with 19 (0·8%) tamoxifen-treated patients (p=0·08). Any effect of treatment on risk of myocardial infarction seemed largely restricted to patients with a history of hypertension; 22 (71·1%) of patients on exemestane who had a myocardial infarction had hypertension at baseline, compared with six (31·6%) of the corresponding patients on tamoxifen. The number of sudden deaths was very low, with three (two cardiac, one unknown cause) in the exemestane and two (one cardiac, one unknown cause) in the tamoxifen group.

Musculoskeletal pain, carpal tunnel syndrome, joint stiffness, paraesthesia, and arthralgia were reported more frequently and cramp less frequently in patients who switched to exemestane than in those who remained on tamoxifen. These effects emerged during the on-treatment period. In total, fractures occurred in 277 patients (table 5). Hip, spine, and wrist fracture rates were few. Including on-treatment and post-treatment follow-up, other types of fractures were more common in patients who switched to exemestane than in those on tamoxifen. Rates of fracture per 1000 women-years (allowing for more than one fracture per patient) were 19·2 (99% CI 15·9–23·1) for exemestane and 15·1 (12·2–18·7) for tamoxifen.

Fewer clinically serious gynaecological events were reported in patients who switched to exemestane than in those on tamoxifen in the on-treatment period and throughout follow-up (tables 4 and 5). The number of gynaecological operations done in each treatment group was low and differences in rates of hysterectomy were not statistically significant. Overall, fewer patients taking exemestane developed uterine polyps or fibroids (odds ratio 0·34, 99% CI 0·19–0·58) or had a dilatation and curettage compared with tamoxifen (0·45, 99% CI 0·19–0·98). Numbers of endometrial cancers did not differ significantly between the groups.



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+=positive. –=negative. ER=oestrogen-receptor. PgR=progesterone-receptor. Forest plots display safety analyses depicting the HR as the centre of the box and 95% CI as a horizontal line, the box size being proportional to the precision of the estimate.

Discussion

This updated analysis of IES lends support to the rationale for switching adjuvant therapy to exemestane after 2–3 years of tamoxifen in postmenopausal patients who remain free of recurrence after treatment for early breast cancer. The parallel nature of the disease-free survival curves after treatment is consistent with the notion of a carry-over effect for the tamoxifen-exemestane switch strategy, similar in size to that seen with tamoxifen alone. We observed no evidence that the early disease-related benefits of the switch strategy are lost once treatment has ceased, but little additional relative gain was noted. The hypothesis that an early improvement in disease-free survival would lead to improved overall survival seems to be correct. Despite the good prognosis and age of this population, our results suggest a modest reduction in the risk of death, with divergence of the risk seen 1–2 years after randomisation and persisting thereafter.

In addition to the ITT analysis, we did a supplementary analysis in which we omitted patients subsequently confirmed to have had oestrogen-receptor-negative tumours. On completion of recruitment, 935 (20%) patients had been entered with unknown oestrogen-receptor status; the steering committee expressed interest in ascertaining oestrogen-receptor status in as many of these patients as possible. The supplementary analysis excluded the small group of patients (n=122) subsequently confirmed to have had oestrogen-receptor-negative tumours (irrespective of progesterone-receptor status), who thus would not have satisfied the trial's eligibility criteria and who would be unlikely to benefit from endocrine therapy.[1] The analysis strategy was agreed prospectively by the trial's IDMC

	Exemestane (n=2320)								Tamoxifen (n=2338)								p
	1	2	3	4	UG	Deaths	Total		1	2	3	4	UG	Deaths	Total		
							Number	100%							Number	100%	
CV events (excluding venous thromboembolic events)	35	18	7	2	306	14	382	16·5	44	15	10	0	273	8	350	15·0	0·16
Ischaemic CV disease	21	16	4	0	140	4	185	8·0	35	15	5	0	105	2	162	6·9	0·17
Hypertension	3	3	2	0	822	0	830	35·8	3	1	3	0	765	0	772	33·0	0·05
Venous thromboembolic events	9	3	6	1	9	0	28	1·2	13	11	16	3	11	0	54	2·3	0·004
Fracture	0	4	1	0	95	0	100	4·3	1	1	0	0	71	0	73	3·1	0·03
Arthritis	20	7	4	0	296	0	327	14·1	15	7	4	1	253	0	280	12·0	0·03
Osteoarthritis	8	3	1	0	190	0	202	8·7	10	1	1	0	162	0	174	7·4	0·113
Arthralgia	204	134	20	1	73	0	432	18·6	137	80	15	2	41	0	275	11·8	<0·0001
Carpal tunnel syndrome	2	8	3	0	51	0	64	2·8	0	0	0	0	7	0	7	0·3	<0·0001
Osteoporosis	1	0	1	0	167	0	169	7·3	1	0	0	0	127	0	128	5·5	0·01
Musculoskeletal pain	214	162	22	4	86	0	488	21·0	187	98	21	3	67	0	376	16·1	<0·0001
Cramp	36	11	1	0	5	0	53	2·3	52	37	2	2	5	0	98	4·2	0·0002
Serious gynaecological events	42	18	8	0	49	0	117	5·9	53	26	3	0	98	0	180	9·0	0·0002
Vaginal bleeding	43	24	8	0	16	0	91	4·6	64	35	3	0	29	0	131	6·5	0·008
Uterine DC	0	0	0	0	12	0	12	0·6	0	0	0	0	29	0	29	1·4	0·009
Vaginal discharge	49	4	0	0	12	0	65	2·8	62	15	2	0	12	0	91	3·9	0·04
Endometrial hyperplasia	0	0	0	0	1	0	1	0·1	1	0	0	0	19	0	20	1·0	<0·0001
Uterine polyp/fibroids	0	1	0	0	23	0	24	1·2	1	0	0	0	64	0	65	3·2	<0·0001
Menopausal symptoms	507	418	118	2	28	0	1073	46·3	499	378	102	0	39	0	1018	43·5	0·06
Hot flashes	500	361	93	1	2	0	957	41·3	481	338	83	1	0	0	903	38·6	0·07
Joint stiffness	27	9	0	0	8	0	44	1·9	14	3	0	0	6	0	23	1·0	0·009
Anxiety	47	34	2	0	57	0	140	6·0	39	22	4	0	48	0	113	4·8	0·07
Depression	51	39	2	0	136	0	228	9·8	32	25	4	0	144	0	205	8·8	0·21
Diarrhoea	54	29	8	1	5	0	97	4·2	31	14	1	1	4	0	51	2·2	0·0001
Dizziness	203	68	9	0	4	0	284	12·2	195	67	12	0	8	0	282	12·1	0·85
Fatigue	327	167	31	0	1	0	526	22·7	340	148	30	0	4	0	522	22·3	0·78
Headaches	271	120	24	0	1	0	416	17·9	241	108	14	0	0	0	363	15·5	0·03
Hypercholesterolaemia	4	2	0	0	160	0	166	7·2	5	0	0	0	136	0	141	6·0	0·12
Insomnia	270	131	41	0	12	0	454	19·6	226	129	29	0	9	0	393	16·8	0·02
Nausea	175	36	10	0	4	0	225	9·7	187	46	13	0	2	0	248	10·6	0·30
Paraesthesia	49	11	2	0	3	0	65	2·8	16	5	0	0	3	0	24	1·0	<0·0001
Sweating	222	154	51	1	0	0	428	18·4	213	146	54	0	0	0	413	17·7	0·49
Pain (excluding musculoskeletal pain)	129	66	10	1	23	0	229	9·9	149	55	9	0	37	0	250	10·7	0·36

Criteria for inclusion of adverse events in table: toxic effects that had >1% point difference between the two treatment groups, ≥10% incidence in either treatment group, or a statistically significant difference between the two treatment groups (p<0·01). This safety population included on-treatment events for all treated patients, censoring at relapse or second primary cancer. Denominator for uterine-related symptoms excluded patients who had a hysterectomy before randomisation: n=1982 for exemestane and n=2008 for tamoxifen treatment group. Some deaths of unknown cause were classified (by RB) conservatively as cardiac deaths for the safety analysis. CV=cardiovascular. UG=ungraded (classed as between grades 2 and 3). DC=dilatation and curettage.

Table 4: **Numbers of toxic effects reported on-treatment, by Common Toxicity Criteria grade**

and steering committee, as was the decision to retain patients in the analysis for whom it was not possible to ascertain oestrogen-receptor status. Although other trials that recruited a substantial number of patients with unknown oestrogen-receptor status have reported results for the specific oestrogen-receptor-positive subgroup,[6] our preference was to exclude patients confirmed to have had oestrogen-receptor-negative tumours for the reasons outlined above. The retention in the analysis of patients with continued unknown receptor status, where the majority can be expected to have oestrogen-receptor-positive cancers, maximises the statistical power of the study.

The findings of IES are consistent with those of the ABCSG-8, ARNO-95, and ITA trials,[9,10] which also assessed a switching strategy, in this case to anastrozole. A meta-analysis of the results of these trials, excluding ineligible patients, confirmed early disease-related benefits associated with a switching strategy.[15] With a median follow-up of 30 months, benefits have been reported for disease-free survival (HR=0·59, 95% CI 0·48–0·74; p<0·001) and overall survival (0·71, 0·52–0·98; p=0·038), giving effect

	Exemestane (n=2320)								Tamoxifen (n=2338)								p
	1	2	3	4	UG	Deaths	Total		1	2	3	4	UG	Deaths	Total		
							Number	100%							Number	100%	
CV events (excluding venous thromboembolic events)	44	20	11	2	378	28	483	20·8	51	24	14	1	327	24	441	18·9	0·09
Ischaemic cardiovascular disease	28	17	7	0	171	6	229	9·9	36	23	6	0	128	7	200	8·6	0·12
Other cardiovascular event	18	5	3	1	225	9	261	11·3	23	4	6	0	222	7	262	11·2	0·96
Hypertension	5	2	2	1	897	0	907	39·1	3	1	4	0	832	0	840	35·9	0·03
Venous thromboembolic events	15	5	8	1	15	1	45	1·9	14	12	21	6	19	0	72	3·1	0·01
Fracture	0	4	1	0	157	0	162	7·0	2	1	1	0	111	0	115	4·9	0·003
Other fracture (excluding hip, spine or wrist fractures)	0	2	1	0	113	0	116	5·0	2	1	1	0	76	0	80	3·4	0·007
Arthritis	25	12	5	0	363	0	405	17·5	21	9	5	1	305	0	341	14·6	0·008
Osteoarthritis	12	7	2	0	242	0	263	11·3	15	3	2	0	207	0	227	9·7	0·07
Arthralgia	225	145	27	1	85	0	483	20·8	180	100	20	3	51	0	354	15·1	<0·0001
Carpal tunnel syndrome	2	8	4	0	51	0	65	2·8	0	0	0	0	10	0	10	0·4	<0·0001
Osteoporosis	1	0	1	0	211	0	213	9·2	1	0	0	0	167	0	168	7·2	0·01
Musculoskeletal pain	253	195	37	6	105	0	596	25·7	234	128	27	3	82	0	474	20·3	<0·0001
Cramp	39	12	1	0	6	0	58	2·5	54	38	2	2	7	0	103	4·4	0·0004
Serious gynaecological events	45	21	11	0	62	0	139	7·0	58	30	5	1	119	0	213	10·6	0·0001
Vaginal bleeding	47	27	11	0	19	0	104	5·2	70	42	4	1	36	0	153	7·6	0·002
Uterine DC	0	0	0	0	16	0	16	0·8	0	0	0	0	36	0	36	1·8	0·006
Vaginal discharge	51	6	0	0	14	0	71	3·1	64	17	2	0	13	0	96	4·1	0·06
Endometrial hyperplasia	0	0	0	0	4	0	4	0·2	1	0	0	0	23	0	24	1·2	0·0002
Uterine polyp/fibroids	0	1	0	0	31	0	32	1·6	2	1	0	0	90	0	93	4·6	<0·0001
Menopausal symptoms	513	431	126	3	36	0	1109	47·8	507	391	112	0	44	0	1054	45·1	0·06
Hot flashes	505	375	100	1	3	0	984	42·4	492	350	89	0	1	0	932	39·9	0·08
Anxiety	51	36	3	0	62	0	152	6·6	44	24	4	0	55	0	127	5·4	0·11
Depression	55	44	5	0	159	0	263	11·3	37	30	5	0	158	0	230	9·8	0·10
Diarrhoea	61	33	9	1	6	0	110	4·7	39	15	3	1	4	0	62	2·7	0·0002
Dizziness	219	87	12	0	4	0	322	13·9	210	82	17	1	9	0	319	13·6	0·82
Fatigue	345	184	38	0	2	0	569	24·5	367	161	32	0	4	0	564	24·1	0·75
Headaches	277	137	27	1	1	0	443	19·1	255	126	19	2	0	0	402	17·2	0·09
Hypercholesterolaemia	8	3	0	1	192	0	204	8·8	7	2	0	0	169	0	178	7·6	0·14
Insomnia	278	146	44	0	14	0	482	20·8	241	144	32	0	9	0	426	18·2	0·03
Nausea	192	42	14	0	5	0	253	10·9	204	51	15	1	2	0	273	11·7	0·41
Paraesthesia	54	11	2	0	3	0	70	3·0	18	6	1	0	3	0	28	1·2	<0·0001
Sweating	227	160	55	1	0	0	443	19·1	217	153	60	0	1	0	431	18·4	0·56
Pain	169	90	13	1	35	0	308	13·3	190	77	12	0	56	0	335	14·3	0·30
Gastric ulcer	3	0	0	0	24	0	27	1·2	0	0	0	0	8	0	8	0·3	0·001

Criteria for inclusion of adverse events in table: toxic effects that had >1% point difference between the two treatment groups, ≥10% incidence in either treatment group, or statistically significant difference between the two treatment groups (p<0·01). This safety population includes on-treatment and post-treatment events for all treated patients, censoring at relapse or second primary cancer. The denominator for uterine-related symptoms excludes patients who had a hysterectomy before randomisation; n=1982 for exemestane and n=2008 tamoxifen treatment group. Some deaths of unknown cause were classified (by RB) conservatively as cardiac deaths for the safety analysis. CV=cardiovascular. UG=ungraded (classed as between grades 2 and 3). DC=dilatation and curettage.

Table 5: **Numbers of toxic effects reported on-treatment and post-treatment, by Common Toxicity Criteria grade**

sizes consistent with those reported in IES. For many patients, however, post-treatment follow-up was short; hence, as in our previous publication,[8] the results are dominated by the on-treatment period. Results of studies with initial monotherapy with an aromatase inhibitor, such as ATAC (anastrozole) and BIG 1-98 (letrozole), showed early disease-related and safety benefits on treatment,[6,7,16] but in the ATAC study, with a median follow-up of 68 months, evidence of an improvement in overall survival was not noted (HR=0·97, 95%CI 0·85–1·12); p=0·70), however, only 60% of all deaths were due to breast cancer. In BIG1-98, with a median follow-up of 51 months, fewer women died in the letrozole group (194, 7·9%) than in the tamoxifen group (211, 8·6%), but this difference was not statistically significant (HR=0·91, 95% CI 0·75–1·11); p=0·35). In the extended adjuvant setting (MA17),[11] a switch to letrozole (compared with placebo) after treatment with tamoxifen showed early disease-related benefits that

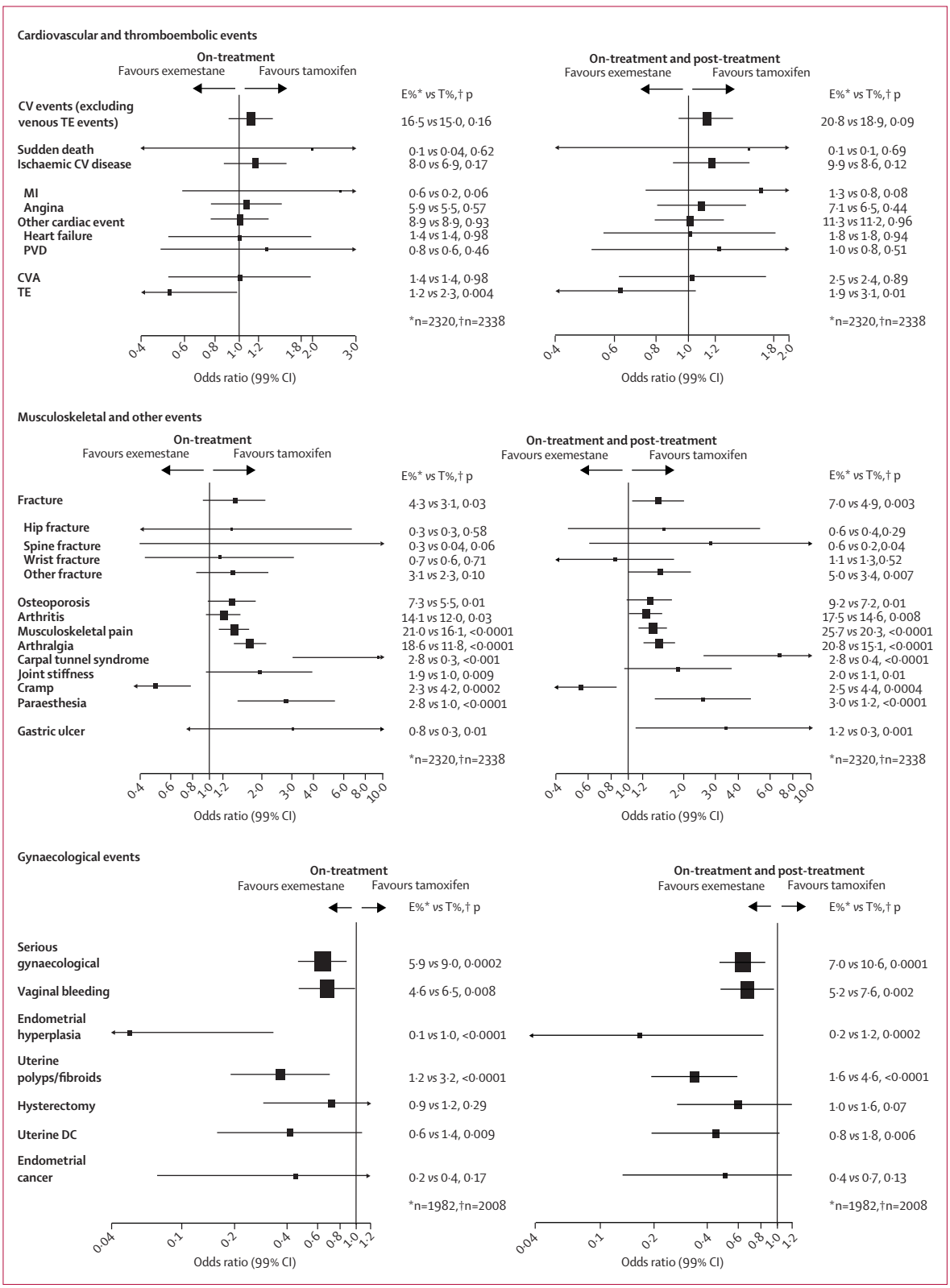

Figure 8: **Forest plots for adverse event data**

E=exemestane. T=tamoxifen. CV=cardiovascular. CVA=cerebrovascular accident. TE=thromboembolic. DC=dilatation and curettage. Forest plots display subgroup analyses depicting the OR as the centre of the box and 99% CI as a horizontal line, the box size being proportional to the precision of the estimate.

resulted in unblinding of the trial while most patients were still on treatment or receiving placebo.[11] Results of updated ITT analyses suggested persistence of a disease-free survival benefit associated with letrozole, despite 73% of patients on placebo crossing over to letrozole, and no effect on overall survival.[17]

No results are available yet from trials that directly compare use of aromatase inhibitor monotherapy with a sequential or switch strategy. Direct evidence from the sequential therapy arms of BIG 1-98 and from the TEAM trial[18] is awaited with keen interest. Caution should be used in the indirect comparison of the monotherapy and switch trials due to confounding associated with the different patient populations and pre-treatment with tamoxifen. Review of major efficacy and safety findings, however, allows an assessment of overall consistency and putative identification of any serious adverse risks. Some authors have attempted to extrapolate from the available trials,[19,20] but their conclusions are in conflict as to which strategy will give the best 10-year outcome, and show the need for direct randomised evidence. Similarly, although MA17 investigated the use of an aromatase inhibitor in the extended adjuvant setting, no direct evidence is available about the potential benefits for continuing treatment with either upfront monotherapy with an aromatase inhibitor or the switch strategy beyond the first 5 years after diagnosis.

With the most mature post-treatment data on treatment with an aromatase inhibitor yet to be published, switching to exemestane seems to have been safe and well tolerated; serious side-effects were rare, and some might be attributable to withdrawal from tamoxifen. A 27% (95% CI 3–58) increase in risk of fracture was noted after the switch to exemestane, attributable to an increase in bone turnover. In the IES bone sub-study,[21] in which changes in bone mineral density were assessed, the median loss of lumbar spine bone mineral density in the exemestane group was 2·9% at 6 months, 3·6% at 12 months, and 4·0% at 24 months. The rate of bone loss associated with exemestane in this study seemed to be partly attenuated by previous treatment with tamoxifen; after the initial rapid rate of bone loss due to the cessation of bone-turnover suppression induced by tamoxifen, the subsequent rate of on-treatment bone loss was thereafter less than 1% per year. Importantly, no patient with a normal bone mineral density at entry to the study became osteoporotic during treatment with exemestane, an observation that has important implications for the follow-up of patients.

The number of patients with myocardial infarction was very low in both treatment groups even tough patients were drawn from a population at risk of adverse cardiac events because of their age. Most patients who developed myocardial infarction after treatment with exemestane had a history of hypertension; emphasising the importance of checking blood pressure. Notably, except for a modest (6–9%) drop in HDL cholesterol, treatment with exemestane has no effect on concentrations of lipids and coagulation factors in plasma in patients with early breast cancer.[22]

The results of IES, in common with other studies, show that patients receiving an aromatase inhibitor have a greater incidence of musculoskeletal complications than do tamoxifen-treated patients. This problem most often occurs in the form of arthralgia or, less commonly, carpal tunnel syndrome. Conversely—and consistent with results of other trials with aromatase inhibitors—a lower incidence of gynaecological complications occurred with exemestane than with tamoxifen, including vaginal bleeding, endometrial hyperplasia, polyps or fibroids, and endometrial cancers. Furthermore, switching to exemestane had no adverse effect on quality of life.[23]

Fewer deaths due to second primary cancers were noted in patients who switched to exemestane compared with those who continued taking tamoxifen, but the reason for this finding is unclear. A chance imbalance is possible, since differentiation of metastatic disease from new primary cancer can be difficult, but independent review of such cases did not result in material changes to the findings. At most, these results are hypothesis-generating.

In summary, switching treatment to exemestane after 2–3 years of tamoxifen improves disease-free survival and translates into a modest reduction in risk of death. This treatment seems to be safe and well tolerated. The findings of IES also show that the benefit of sequential administration of tamoxifen and an aromatase inhibitor in patients with endocrine-responsive breast cancer persists for some years after discontinuation of the aromatase inhibitor. These results seem to be independent of any tumour characteristics that we have measured; however future research should investigate whether molecular markers exist that predict which patients benefit from which endocrine treatment strategy.

Contributors

R C Coombes, principal investigator and chair of the steering committee, was responsible for the trial design, trial management, data interpretation, and manuscript writing. J M Bliss, principal statistician and member of the steering committee, was responsible for trial management and, with R C Coombes, for the trial design, data interpretation, and manuscript writing, and oversaw all statistical analyses. L S Kilburn, trial statistician and member of the steering committee, did the main analyses and took part in manuscript writing. C F Snowdon, member of the steering committee, was responsible for trial management at the coordinating data centre and took part in the preparation of data for analysis and manuscript writing. R Paridaens, co-chair of the study and member of the steering committee, helped interpret the data. R E Coleman, chair of the bone sub-protocol and member of the steering committee, took part in data interpretation and manuscript writing. S E Jones, J Jassem, P E Lonning, T Delozier, I Alvarez, J F Forbes, A S Coates, L Del Mastro, O Ortmann, K Diedrich, G Cocconi, S B Holmberg, A Stewart, M Carpentieri, E Colajori, and M Subar are members of the steering committee and took part in data interpretation and manuscript writing. C J H Van de Velde, D Dodwell, E Mickiewicz, J Andersen, M Castiglione, N Stuart, and E Bajetta are members of the steering committee and helped interpret the data. L J Fallowfield is chair of the quality of life sub-study and a member of the steering committee, and took part in data interpretation and manuscript writing. G Bertelli is chair of the

endometrial sub-protocol and a member of the steering committee, and took part in data interpretation and manuscript writing. R G Bogle provided expert advice on the classification and interpretation of cardiovascular events. E Hall (member of the steering committee) and E Ireland took part in the statistical analysis, data interpretation and manuscript writing. All contributors have seen and approved the final version of the manuscript.

Conflict of interest statement

R C Coombes has received research grants and honoraria from Pfizer. R Paridaens has received honoraria and travel awards from Pfizer. R E Coleman has received honoraria for advisory panels and speaking engagements from Pfizer. S E Jones has received honoraria and consultancy fees from Pfizer. O Ortmann has received research grants, consultancy fees and speaker honoraria from Pfizer, Novartis and AstraZeneca. A S Coates has received travel awards from Pfizer. S B Holmberg has received speaker honoraria from Pfizer, Novartis, and AstraZeneca. P E Lønning has received speaker honoraria from AstraZeneca, Pfizer, and Novartis. J Forbes has received honoraria for advisory board participation from Eli Lilly, Novartis, and AstraZeneca. L J Fallowfield has received honoraria and consultancy fees from AstraZeneca, Novartis, and Pfizer. G Bertelli has received travel awards from Pfizer. M Carpentieri, E Colajori, and M Subar are employees of Pfizer. J M Bliss has received honoraria, travel grants, and research funds from Pfizer.

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