Adjuvant anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, in endocrine-sensitive breast cancer (FATA-GIM3): a randomised, phase 3 trial

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Summary

Background Uncertainty exists about the optimal schedule of adjuvant treatment of breast cancer with aromatase inhibitors and, to our knowledge, no trial has directly compared the three aromatase inhibitors anastrozole, exemestane, and letrozole. We investigated the schedule and type of aromatase inhibitors to be used as adjuvant treatment for hormone receptor-positive early breast cancer.

Methods FATA-GIM3 is a multicentre, open-label, randomised, phase 3 trial of six different treatments in postmenopausal women with hormone receptor-positive early breast cancer. Eligible patients had histologically confirmed invasive hormone receptor-positive breast cancer that had been completely removed by surgery, any pathological tumour size, and axillary nodal status. Key exclusion criteria were hormone replacement therapy, recurrent or metastatic disease, previous treatment with tamoxifen, and another malignancy in the previous 10 years. Patients were randomly assigned in an equal ratio to one of six treatment groups: oral anastrozole (1 mg per day), exemestane (25 mg per day), or letrozole (2·5 mg per day) tablets upfront for 5 years (upfront strategy) or oral tamoxifen (20 mg per day) for 2 years followed by oral administration of one of the three aromatase inhibitors for 3 years (switch strategy). Randomisation was done by a computerised minimisation procedure stratified for oestrogen receptor, progesterone receptor, and HER2 status; previous chemotherapy; and pathological nodal status. Neither the patients nor the physicians were masked to treatment allocation. The primary endpoint was disease-free survival. The minimum cutoff to declare superiority of the upfront strategy over the switch strategy was assumed to be a 2% difference in disease-free survival at 5 years. Primary efficacy analyses were done by intention to treat; safety analyses included all patients for whom at least one safety case report form had been completed. Follow-up is ongoing. This trial is registered with the European Clinical Trials Database, number 2006-004018-42, and ClinicalTrials.gov, number NCT00541086.

Findings Between March 9, 2007, and July 31, 2012, 3697 patients were enrolled into the study. After a median follow-up of 60 months (IQR 46–72), 401 disease-free survival events were reported, including 211 (11%) of 1850 patients allocated to the switch strategy and 190 (10%) of 1847 patients allocated to upfront treatment. 5-year disease-free survival was 88·5% (95% CI 86·7–90·0) with the switch strategy and 89·8% (88·2–91·2) with upfront treatment (hazard ratio 0·89, 95% CI 0·73–1·08; p=0·23). 5-year disease-free survival was 90·0% (95% CI 87·9–91·7) with anastrozole (124 events), 88·0% (85·8–89·9) with exemestane (148 events), and 89·4% (87·3 to 91·1) with letrozole (129 events; p=0·24). No unexpected serious adverse reactions or treatment-related deaths occurred. Musculoskeletal side-effects were the most frequent grade 3–4 events, reported in 130 (7%) of 1761 patients who received the switch strategy and 128 (7%) of 1766 patients who received upfront treatment. Grade 1 musculoskeletal events were more frequent with the upfront schedule than with the switch schedule (924 [52%] of 1766 patients *vs* 745 [42%] of 1761 patients). All other grade 3–4 adverse events occurred in less than 2% of patients in either group.

Interpretation 5 years of treatment with aromatase inhibitors was not superior to 2 years of tamoxifen followed by 3 years of aromatase inhibitors. None of the three aromatase inhibitors was superior to the others in terms of efficacy. Therefore, patient preference, tolerability, and financial constraints should be considered when deciding the optimal treatment approach in this setting.

Funding Italian Drug Agency.

Introduction

For many years, tamoxifen has been the adjuvant treatment of choice for postmenopausal women with hormone-responsive early breast cancer; 5 years of treatment reduces the risk of recurrence by 47% and the risk of death by 26%.[1] However, increased incidence of

Research in context

Evidence before this study

We searched PubMed without language restrictions up to Aug 30, 2017, using the search terms "early breast cancer", "adjuvant treatment", and "anastrozole or exemestane or letrozole" to identify meta-analyses and prospective trials of adjuvant endocrine treatment of postmenopausal women with breast cancer. We identified one Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis on the efficacy of adjuvant treatment with tamoxifen and aromatase inhibitors; two international trials—the BIG1-98 study (with letrozole) and TEAM study (with exemestane)—comparing switch with upfront schedules; and two trials that did head-to-head comparisons of anastrozole and exemestane (MA.27 study) or letrozole (FACE trial; node-positive patients only). These studies showed that tamoxifen given for 5 years reduced the annual risk of recurrence by 47% and the risk of death by 26%. Aromatase inhibitors reduced annual recurrence by about 30% compared with tamoxifen, and an aromatase inhibitor given for 5 years reduced 10-year breast cancer mortality by about 15% compared with 5 years of tamoxifen. Tamoxifen followed by letrozole was similarly effective to letrozole alone (BIG1-98), and tamoxifen followed by exemestane was similarly effective to exemestane alone (TEAM). Treatment with exemestane for 5 years was not better than anastrozole for 5 years (MA.27), and letrozole for 5 years was not better than anastrozole for 5 years in the treatment of node-positive patients (FACE).

Added value of this study

To our knowledge, no trial has used anastrozole when directly comparing the switch schedule with the upfront schedule, and no direct evidence is available that compares exemestane with letrozole and, more broadly, the three aromatase inhibitors among themselves. Thus, FATA-GIM3 contributes important data to the comparisons of the upfront schedule (5 years of aromatase inhibitors) with the switch schedule (2 years of tamoxifen followed by 3 years of aromatase inhibitors), and among the three aromatase inhibitors.

Implications of all the available evidence

The available evidence shows that the absolute difference between 5 years of aromatase inhibitors and 2 years of tamoxifen then aromatase inhibitors for 3 years is small in terms of clinical relevance, and that efficacy does not differ between the three aromatase inhibitors. Therefore, patient preference, tolerability, and financial constraints should be considered when choosing which schedule and which aromatase inhibitor to include in the therapeutic plan for adjuvant hormonal treatment of postmenopausal patients with early breast cancer.

endometrial cancer, thromboembolic disorders, hot flushes, mood disorders, and vaginal symptoms have been reported as notable side-effects of tamoxifen.[1,2]

Three aromatase inhibitors, either non-steroidal (anastrozole and letrozole) or steroidal (exemestane), have been shown to improve the efficacy of adjuvant endocrine treatment if used in place of or sequentially with tamoxifen. However, all aromatase inhibitors cause adverse events of arthralgia, bone pain, and osteoporosis.[3–9]

In 2006, when the First Adjuvant Trial on All Aromatase Inhibitors (FATA-GIM3) was planned, whether aromatase inhibitors should be used upfront or after 2 years of tamoxifen treatment was highly debated. A possible beneficial effect on disease-free survival during the first 2 years of treatment favoured the upfront strategy;[10] by contrast, indirect comparisons of trials testing the switch strategy with trials testing the upfront strategy suggested a greater benefit with the sequential strategy because of possible lower induction of drug-resistant phenotypes.[11] Additionally, musculoskeletal and cardiac toxicity were considered more likely to occur with longer exposure to aromatase inhibitors (ie, with upfront treatment), but, after the ATAC study[3]—the first large trial to be published in this field—the upfront strategy with anastrozole was regarded as standard practice. Simulations and modelling approaches have shown conflicting results, although they suggested relevant clinical and economic implications depending on the schedule used.[10,11] Furthermore, whether or not differences existed among different types of aromatase inhibitors, either in terms of efficacy or side-effects, was uncertain because they had never been compared directly in a single trial.

Therefore, the FATA-GIM3 trial was planned to test whether or not upfront treatment with aromatase inhibitors was more effective than the sequential treatment approach and to directly compare (to our knowledge, for the first time) anastrozole versus exemestane versus letrozole.

Methods

Study design and participants

FATA-GIM3 is a multicentre, open-label, randomised, 2×3 factorial phase 3 trial done in 76 public institutions in Italy. Eligible patients were postmenopausal women of any age with histologically confirmed invasive breast cancer that had been completely removed by surgery, with any pathological tumour size and any axillary nodal status according to the 2003 American Joint Committee on Cancer staging system.[12] For women younger than 60 years, absence of menses for more than 1 year or follicle-stimulating hormone concentrations within the postmenopausal range were required. Women who had previously undergone bilateral oophorectomy were also eligible. The primary tumour had to score positive for oestrogen receptor or progesterone receptor status (≥10% of tumour cells positive in immunohistochemistry or ≥10 fmol/mg cytosol protein in ligand-binding assay). Adjuvant or neoadjuvant chemotherapy, if given, had to be

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See **Online** for appendix

completed before enrolment. Patients with any HER2 status were eligible, although those with HER2-positive tumours had to be treated with trastuzumab according to the authorised schedule.

Patients were excluded in cases of hormone-replacement therapy either at or during the month before randomisation; recurrent or metastatic disease discovered during baseline staging; HER2-positive tumours if treatment with trastuzumab was not feasible; previous treatment with tamoxifen; another malignancy (breast cancer or invasive cancer other than basal-cell carcinoma of the skin or carcinoma in situ of the cervix) in the previous 10 years; concomitant severe disease that contraindicated adjuvant endocrine treatment or would place the patient at high risk of toxicity with the study drugs; and treatment with other experimental drugs either at or during the month before randomisation.

All participants provided written informed consent. The protocol was approved by the ethics committees at each of the participating institutions. The trial met requirements of the Italian Drug Agency for independent clinical trials planned to improve clinical practice. The study protocol is in the appendix.

Randomisation and masking

Patients were equally allocated (in a 1:1:1:1:1:1 ratio) to one of the six study groups via centralised web-based randomisation hosted on the GIM group website with a computerised minimisation procedure stratified for oestrogen receptor and progesterone receptor status (both positive *vs* one positive and one negative *vs* one positive and one unknown), HER2 status (positive [defined as 3+ at immunohistochemistry or positive by fluorescence in-situ hybridisation] *vs* negative *vs* unknown), previous chemotherapy (none *vs* adjuvant *vs* neoadjuvant *vs* ajuvant and neoadjuvant), and pathological nodal status (pN0 *vs* pN1 *vs* pN2 *vs* pN3). This trial was open label, and patients and clinical staff were aware of treatment assignment. Individuals who did the statistical analyses were masked to treatment allocation.

For the **GIM group website** see https://www.oncotech.org/gim/home/

Procedures

Patients received oral anastrozole (1 mg), exemestane (25 mg), or letrozole (2·5 mg) tablets once per day for 5 years (upfront strategy) or once per day for 3 years after 2 years of treatment with oral tamoxifen tablets (20 mg once per day; switch strategy). All study drugs were included in the Italian national formulary and reimbursed by the National Health System. Treatment could be temporarily suspended because of side-effects or other intercurrent reasons. The length of treatment interruption was not limited a priori, but it was advised to be as short as possible. If the same treatment could not be resumed, patients definitively interrupting tamoxifen were switched to the aromatase inhibitor that had been assigned at randomisation, whereas patients interrupting aromatase inhibitors could receive tamoxifen as alternative treatment, with a switch to a different aromatase inhibitor being prohibited.

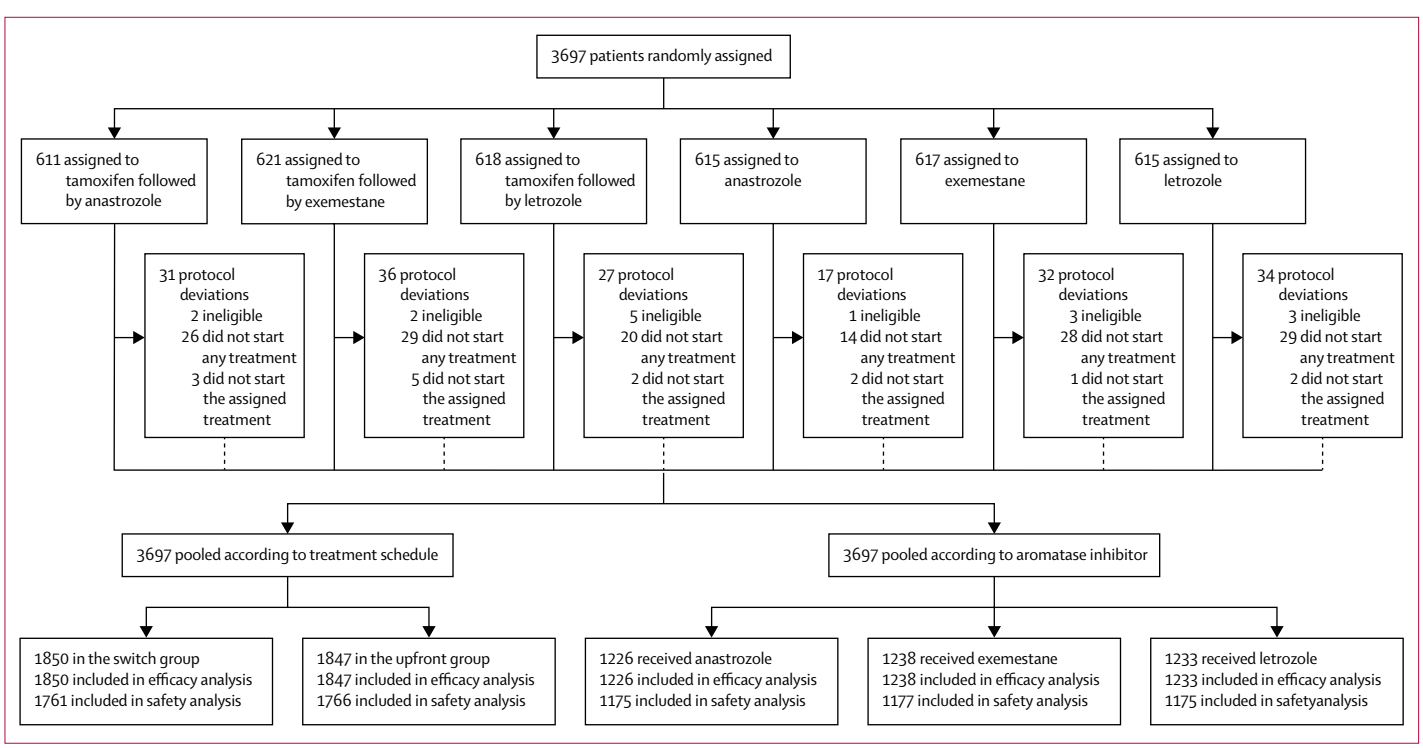

Figure 1: **Trial profile**

Permanent discontinuation could occur according to investigator's clinical judgment, unacceptable toxicity, patient's choice, or disease recurrence.

If indicated according to standard guidelines, locoregional radiotherapy was administered either before or after randomisation, concurrently with the study drugs. Trastuzumab was prescribed to patients with HER2-positive tumours, according to accepted schedule and indication. Hormone replacement therapy was prohibited. Bisphosphonates were not allowed prophylactically to prevent osteoporosis, but could be prescribed to treat osteoporosis, if indicated, according to current practice.

Baseline staging included physical examination, blood chemistry, and electrocardiogram (ECG) within 1 month before randomisation; chest radiograph and liver ultrasound or CT scan within 3 months before randomisation; and mammography and bone scan within 1 year before randomisation. During treatment, visits and blood chemistry were planned every 6 months up to 5 years after randomisation, then yearly; chest radiograph and liver ultrasound or CT scans were planned every 6 months for 3 years, then yearly; and ECG, mammography, and bone scan were planned yearly. Gynaecological examination and measurement of bone mineral density were left to the choice of investigators at participating centres, but data were collected.

Outcomes

The primary endpoint was disease-free survival, defined according to the Standardized Definitions for Efficacy End Points (STEEP) system[13] as the time from randomisation to locoregional or distant recurrence, contralateral invasive breast cancer, ductal carcinoma in situ, second malignancy other than breast, or death from any cause (whichever occurred first). No central review was done. Secondary endpoints reported in this paper are overall survival, defined as the time from randomisation to death from any cause, and toxicity, assessed according to Common Terminology Criteria for Adverse Events version 3.0. Toxicity was assessed at every visit for 5 years. Other secondary efficacy endpoints according to the STEEP system (ie, invasive-disease-free survival, distant-disease-free survival, distant-recurrence-free survival, relapse-free survival, recurrence-free interval, breast-cancer-free interval, distant-recurrence-free interval) and the effects of treatment on lipid profile will be reported separately when a greater number of events have been recorded.

Statistical analysis

We calculated sample size using EAST software version 5, assuming that a 2% difference in disease-free survival at 5 years was the minimum clinically significant cutoff required to conclude that the upfront strategy was more effective than the switch strategy. At initial planning in July, 2006, based on comparisons of the switch strategy versus upfront tamoxifen, the expected 5-year disease-free survival with the switch strategy was estimated to be 85%, corresponding to a hazard ratio (HR) of 0·86. Therefore, with a two-sided α value of 0·05, a power of 80%, and on the basis of one interim futility analysis, 1354 events were required and enrolment of about 10 000 patients was planned. In 2009, after presentation of long-term data from the ABCSG trial 8 at the 2008 San Antonio Breast Cancer Symposium, the expected 5-year disease-free survival in the switch group was increased to 90% (protocol amendment 1; October, 2009) and the HR decreased to 0·79. With a two-sided p value of 0·05, a power of 80%, and on the basis of three interim futility analyses, a maximum of 669 events was required

	Treatment schedule		Aromatase inhibitor		
	Switch (n=1850)	Upfront (n=1847)	Anastrozole (n=1226)	Exemestane (n=1238)	Letrozole (n=1233)
Age, years					
Median (IQR)	64 (58–70)	64 (57–70)	64 (58–70)	64 (58–70)	63 (58–71)
<60	556 (30%)	596 (32%)	391 (32%)	365 (29%)	396 (32%)
60–69	768 (42%)	742 (40%)	504 (41%)	523 (42%)	483 (39%)
≥70	526 (28%)	509 (28%)	331 (27%)	350 (28%)	354 (29%)
Type of menopause					
>60 years or oophorectomy	1309 (71%)	1271 (69%)	842 (69%)	885 (71%)	853 (69%)
<60 years and >1 year amenorrhoea	398 (22%)	432 (23%)	296 (24%)	248 (20%)	286 (23%)
<60 years and <1 year amenorrhoea*	75 (4%)	69 (4%)	47 (4%)	45 (4%)	52 (4%)
<60 years, unknown amenorrhoea	68 (4%)	75 (4%)	41 (3%)	60 (5%)	42 (3%)
Body-mass index					
Median (IQR), kg/m²	27·0 (24·0–30·8)	26·6 (23·9–30·4)	26·8 (24·0–30·8)	26·6 (23·8–30·4)	27·0 (23·9–30·8)
Underweight or normal	503 (27%)	528 (29%)	326 (27%)	366 (30%)	339 (27%)
Overweight	537 (29%)	568 (31%)	388 (32%)	357 (29%)	360 (29%)
Obese	432 (23%)	410 (22%)	285 (23%)	269 (22%)	288 (23%)
Unknown	378 (20%)	341 (18%)	227 (19%)	246 (20%)	246 (20%)
Hormone receptor (oestrogen receptor and progesterone receptor) status					
Both positive	1646 (89%)	1642 (89%)	1094 (89%)	1099 (89%)	1095 (89%)
Only one positive	204 (11%)	205 (11%)	132 (11%)	139 (11%)	138 (11%)
HER2 status					
Negative	1663 (90%)	1669 (90%)	1105 (90%)	1114 (90%)	1113 (90%)
Positive	168 (9%)	162 (9%)	107 (9%)	114 (9%)	109 (9%)
Unknown	19 (1%)	16 (1%)	14 (1%)	10 (1%)	11 (1%)
Pathological nodal status					
pN0	1191 (64%)	1187 (64%)	788 (64%)	799 (65%)	791 (64%)
pN1	465 (25%)	463 (25%)	311 (25%)	308 (25%)	309 (25%)
pN2 or pN3	194 (10%)	197 (11%)	127 (10%)	131 (11%)	133 (11%)
Pathological tumour category					
pT1	1299 (70%)	1287 (70%)	863 (70%)	856 (69%)	867 (70%)
pT2	446 (24%)	447 (24%)	296 (24%)	306 (25%)	291 (24%)
pT3 or pT4	45 (2%)	46 (2%)	33 (3%)	24 (2%)	34 (3%)
Unknown	60 (3%)	67 (4%)	34 (3%)	52 (4%)	41 (3%)

(Table 1 continues on next page)

	Treatment schedule		Aromatase inhibitor		
	Switch (n=1850)	Upfront (n=1847)	Anastrozole (n=1226)	Exemestane (n=1238)	Letrozole (n=1233)
(Continued from previous page)					
Histological grading					
Low	242 (13%)	243 (13%)	169 (14%)	152 (12%)	164 (13%)
Intermediate	1060 (57%)	1069 (58%)	708 (58%)	699 (56%)	722 (59%)
High	407 (22%)	390 (21%)	256 (21%)	281 (23%)	260 (21%)
Unknown	141 (8%)	145 (8%)	93 (8%)	106 (9%)	87 (7%)
Previous chemotherapy					
None	1138 (62%)	1144 (62%)	757 (62%)	764 (62%)	761 (62%)
Adjuvant	665 (36%)	658 (36%)	438 (36%)	444 (36%)	441 (36%)
Neoadjuvant	47 (3%)	45 (2%)	31 (3%)	30 (2%)	31 (3%)
Previous or concurrent trastuzumab					
No	1660 (90%)	1663 (90%)	1107 (90%)	1100 (89%)	1116 (91%)
Yes	131 (7%)	126 (7%)	88 (7%)	88 (7%)	81 (7%)
Unknown	59 (3%)	58 (3%)	31 (3%)	50 (4%)	36 (3%)
Previous or concurrent radiotherapy					
No	544 (29%)	536 (29%)	394 (32%)	334 (27%)	352 (29%)
Yes	1247 (67%)	1253 (68%)	801 (65%)	854 (69%)	845 (69%)
Unknown	59 (3%)	58 (3%)	31 (3%)	50 (4%)	36 (3%)

Data are n (%), unless otherwise specified. *Postmenopausal follicle-stimulating hormone concentrations.

Table 1: **Baseline characteristics**

and a sample size of 3600 patients was planned. Interim futility analyses were planned to reject the alternative hypothesis only, according to a β-spending function with a Pocock boundary. Applying the same parameters, 792 events were required for the log-rank comparison of the three aromatase inhibitors, according to the Ahnn and Anderson approach.[14] We focused on main effects rather than on interaction because there was no suggestion in published literature that schedule effect would change across aromatase inhibitors. We planned to compare the aromatase inhibitors when the result of the primary comparison between schedules became available.

The first futility interim analysis, done in May, 2015, with 318 events, did not lead to early stopping of the trial. In 2015, after publication of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis,[15] and because of the length of time still required to reach the planned number of events, the independent data monitoring committee suggested that we do the two final analyses at a median follow-up of 5 years, independently of the number of events. Follow-up and data collection, however, will continue, with no defined closure date.

Efficacy analyses were done by intention to treat (all randomly assigned patients) and safety analyses included all patients for whom at least one safety case report form had been completed. In the comparative analysis of schedules, we did the primary analysis of disease-free survival with a multivariable Cox model including stratification variables of hormone receptor status, HER2 status, previous chemotherapy, pathological nodal status, aromatase inhibitor, and centre size (three categories according to tertiles of the number of patients enrolled) as covariates. We checked the proportionality assumption by entering a time-dependent covariate of treatment×log(time) interaction. We tested first-order interactions between treatment (schedule [two categories] and aromatase inhibitor [three categories] and covariates with the likelihood-ratio test of two nested models, with and without interaction; the effect of treatments by subgroup was reported as HR and 95% CI in a forest plot. Such analyses were protocol-specified for stratification variables (oestrogen receptor and progesterone receptor status, HER2 status, previous chemotherapy, and pathological nodal status) or decided post hoc for consistency with relevant published literature for age, type of menopause, body-mass index, tumour size, histological grade, previous trastuzumab, and previous radiotherapy.

For the comparison of the three aromatase inhibitors, the global null hypothesis of treatment equivalence had to be first tested with the log-rank test; only in case of significance at the 0·05 level did we plan to do pairwise comparisons between aromatase inhibitors with Bonferroni-Holm adjustment.[16]

Disease-free survival and overall survival were estimated with the Kaplan-Meier method.

For toxicity analyses, for each patient and for each type of toxicity, we calculated the worst event suffered and reported them as the occurrence of either any toxicity (grade 1 or worse) or severe toxicity (grade 3 or 4). The complete toxicity distribution (ie, all grades suffered) was used for statistical comparisons. In both comparisons (strategies and aromatase inhibitors), analyses were done with the Kruskal–Wallis non-parametric ANOVA with significance level of 0·01. If the overall comparison of aromatase inhibitors was significant, pairwise comparisons between aromatase inhibitors were done with the Kruskal–Wallis test using Bonferroni-Holm adjustment; the three α levels for sequential testing were 0·0033, 0·005, and 0·01. We used Stata/MP for Windows (version 14.2) for all statistical analyses.

This study is registered with the European Clinical Trials Database, number 2006-004018-42, and ClinicalTrials.gov, number NCT00541086.

Role of the funding source

The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between March 9, 2007, and July 31, 2012, 3697 eligible patients were enrolled at 76 centres in Italy (figure 1). Baseline characteristics of patients are summarised by treatment schedule strategy and by drug in table 1 and by treatment group in the appendix (pp 2–3). Information

about baseline metabolic profile, comorbidities, and bone health status are also in the appendix (pp 4–6). The median age of all enrolled patients was 64 years (IQR 58–71), the primary tumour was pT1 in 2586 (70%) of 3697 patients; axillary lymph nodes were pathologically negative in 2378 (64%), and 330 (9%) of 3697 tumours were HER2 positive. Adjuvant or neoadjuvant chemotherapy had been given to 1415 (38%) of the patients before randomisation. All baseline characteristics were well balanced among the study groups.

At a median follow-up of 60 months (IQR 46–72), 401 disease-free survival events (211 with the switch schedule and 190 with the upfront schedule) and 138 deaths (80 with the switch schedule and 58 with the upfront schedule) had been reported. 53 of the patients who died did not have cancer when they died (table 2). 85 patients had been diagnosed with second non-breast cancer, five of whom were diagnosed after breast cancer recurrence (table 2; appendix p 7). Breast cancer was the most frequent cause of death, both in patients who received the switch treatment (55 [3%] of 1850 patients) and in those treated upfront (30 [2%] of 1847 patients).

At 5 years, disease-free survival was 88·5% (95% CI 86·7–90·0) with the switch schedule and 89·8% (88·2–91·2) with upfront treatment (HR 0·89, 95% CI 0·73–1·08; p=0·23; figure 2A). 5-year overall survival was 95·3% (95% CI 94·1–96·3) with the switch schedule and 96·8% (95·7–97·6) with the upfront schedule (HR 0·72, 95% CI 0·51–1·00; p=0·052; figure 2B).

Disease-free survival at 5 years was 90·0% (95% CI 87·9–91·7) with anastrozole (124 events), 88·0% (85·8–89·9) with exemestane (148 events), and 89·4% (87·3–91·1) with letrozole (129 events; p=0·24; figure 3A, appendix p 8). Since the overall comparison of the three aromatase inhibitors was not significant, pairwise comparisons between aromatase inhibitors were not done. For description only, the HR for progression or death was 1·24 (95% CI 0·97–1·57) for exemestane versus anastrozole and 1·05 (0·82–1·35) for letrozole versus anastrozole (appendix p 10). The interaction test between schedule and aromatase inhibitor used was not significant ($p_{interaction}$=0·26; appendix pp 9–10). At 5 years, overall survival was 95·9% (95% CI 94·4–97·0) with anastrozole (43 deaths), 95·7% (94·2–96·8) with exemestane (52 deaths), and 96·6% (95·3–97·6) with letrozole (43 deaths; p=0·52; figure 3B).

In a prespecified analysis, patient and tumour characteristics at baseline did not significantly interact with treatment effect (HR of progression or death) in either comparison (switch *vs* upfront strategy or anastrozole *vs* exemestane *vs* letrozole; appendix pp 9–11).

Median time on tamoxifen was 24 months (IQR 23–25); median time on treatment was similar for the three aromatase inhibitors (32 months [IQR 28–36] to 35 months [30–36] in the switch group and 54 months [52–60] to 56 months [53–60] in the upfront group; appendix p 12). Toxicity was the main reason for early treatment interruption (appendix p 13), and was more frequent with tamoxifen (204 [11%] of 1850 patients) than with aromatase inhibitors (93 [5%] of 1850 patients in the switch group and 131 [7%] of 1847 patients in the upfront group). Endometrial side-effects were the most frequent

	Treatment schedule		Aromatase inhibitor		
	Switch (n=1850)	Upfront (n=1847)	Anastrozole (n=1226)	Exemestane (n=1238)	Letrozole (n=1233)
Disease-free survival event	211	190	124	148	129
Type of first disease-free survival event					
Locoregional	30/211 (14%)	26/190 (14%)	12/124 (10%)	30/148 (20%)	14/129 (11%)
Distant	99/211 (47%)	84/190 (44%)	63/124 (51%)	57/148 (39%)	63/129 (49%)
Second breast cancer	13/211 (6%)	16/190 (8%)	12/124 (10%)	11/148 (7%)	6/129 (5%)
Second non-breast cancer	44/211 (21%)	36/190 (19%)	26/124 (21%)	29/148 (20%)	25/129 (19%)
Death without any cancer	25/211 (12%)	28/190 (15%)	11/124 (9%)	21/148 (14%)	21/129 (16%)
Second non-breast cancers					
Colorectal	9	13	8	7	7
Endometrial	10	3	4	4	5
Pulmonary	3	5	4	2	2
Pancreatic	5	2	3	3	1
Haematological	3	3	1	4	1
Renal	3	2	2	1	2
Ovarian	4	1	1	1	3
Hepatic	4	0	1	2	1
Melanoma	2	1	0	2	1
Urinary	1	2	0	2	1
Other	3	6	3	4	2
Deaths	80	58	43	52	43

Table 2: **Distribution of events**

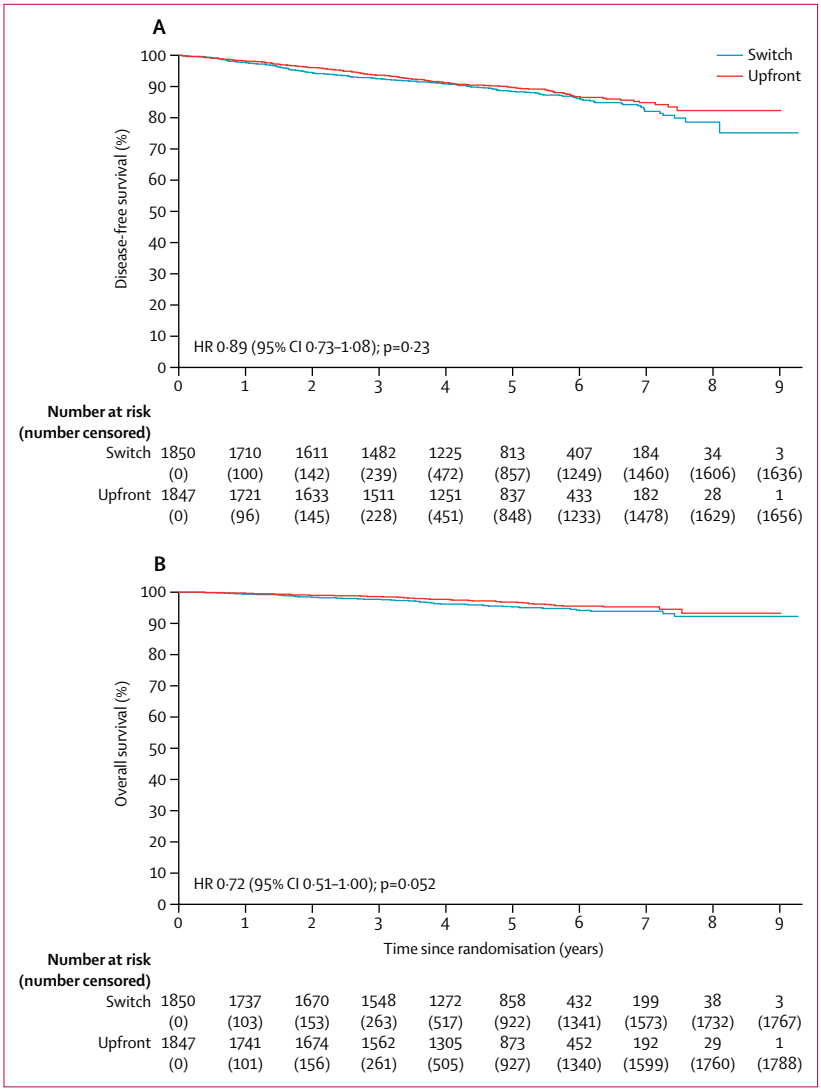

Figure 2: **Disease-free survival (A) and overall survival (B) according to schedule**
HR=hazard ratio.

reason for tamoxifen interruption (66 [4%] of 1850 patients), whereas musculoskeletal side-effects were the main reason for interruption of aromatase inhibitors (53 [3%] of 1850 patients in the switch group and 76 [4%] of 1847 patients in the upfront group).

Toxicity data were not available for 170 (5%) of 3697 patients, and the proportion of missing data was similar across comparison groups (appendix pp 14–19). Details of toxicity data by treatment group are reported in the appendix (pp 14–19). No unexpected serious adverse events or treatment-related deaths occurred. Tables 3 and 4 summarise toxicity data by comparison group, according to planned significance rules. Musculoskeletal side-effects (including osteoporosis, arthritis, muscle weakness, pain) were the most frequent grade 3–4 events, reported in 130 (7%) of 1761 patients in the switch group and 128 (7%) of 1766 patients in the upfront group. The overall frequency of musculoskeletal events (ie, including grades 1 and 2) was significantly different between the switch and upfront groups because of a higher incidence of grade 1 events in the upfront group than in the switch group (924 [52%] of 1766 patients *vs* 745 [42%] of 1761 patients). Apart from muscoloskeletal events, all other grade 3–4 events occurred in less than 2% of patients in either group; grade 3–4 cardiac side-effects were reported in 19 (1%) of 1761 patients in the switch group and in 23 (1%) of 1766 patients in the upfront group. Overall, hot flushes, hypertriglyceridaemia, and vaginal, vascular, and endometrial adverse events were more frequent with the switch schedule than with the upfront schedule, whereas hypercholesterolaemia and neurological symptoms were more frequent with the upfront schedule than with the switch schedule (table 3). Bone fractures were reported in 95 (5%) of 1761 patients in the switch group and in 74 (4%) of 1766 patients in the upfront group (table 3; appendix pp 14–19). Additionally, when analysing adverse events by type of aromatase inhibitor, gastrointestinal side-effects were more frequent with exemestane than with letrozole, and hypercholesterolaemia was more frequent with anastrozole and letrozole than with exemestane (table 4). All other side-effects were not significantly different among the three aromatase inhibitors.

Discussion

In this trial, we investigated whether upfront treatment (ie, 5 years of aromatase inhibitors) was more effective than a switch schedule, wherein aromatase inhibitors were administered after 2 years of tamoxifen. We did not find upfront treatment to be superior to the switch schedule, assuming a minimum clinically significant difference in 5-year disease-free survival of 2%. The absolute difference between the disease-free-survival curves during the 5 years did not reach the 2% threshold, with a maximum difference between the groups of 1·6% after 2 years. Additionally, we did not find significant heterogeneity in schedule effect across major patient subgroups. The number of deaths and other breast-related events was too low to allow reliable conclusions to be drawn on endpoints other than disease-free survival.

Two other trials of direct comparisons of upfront versus sequential treatment were published while FATA-GIM3 was ongoing: one with letrozole (the BIG 1-98 trial)[17] and one with exemestane (the TEAM trial).[18,19] Neither trial found a significant difference between the two schedules, and both studies concluded that either strategy is an appropriate treatment option. However, the EBCTCG meta-analysis[15] of these two trials plus another small study done in Italy found that disease-free survival was significantly different between the strategies, in favour of the upfront strategy, although with a small absolute benefit (1·1% at 5 years of follow-up, declining to 0·7% at 7 years; HR 0·90, 95% CI

0·81–0·99; p=0·045). We argue that such absolute differences are not clinically relevant. Therefore, physicians might reasonably present 5 years of aromatase inhibitors or 2 years of tamoxifen then aromatase inhibitors up to 5 years as similarly effective strategies and discuss with the patient the toxicity profile as a possible driver of choice. Our data confirm that musculoskeletal symptoms are the most common side-effects of aromatase inhibitors, occurring in more than half of patients and more frequently with the upfront schedule than with the switch schedule because of longer exposure to aromatase inhibitors. The opportunity to include patient preference and tolerability of therapy in the decision-making process was also highlighted by the 2017 St Gallen panelists,[20] given the overall modest differences in outcomes between tamoxifen and aromatase inhibitors.

To our knowledge, FATA-GIM3 is the first trial to directly compare the three aromatase inhibitors anastrozole, exemestane, and letrozole as adjuvant treatments for hormone receptor-positive breast cancer. We found no significant difference in the three-group comparisons and, therefore, did not proceed to formal head-to-head pairwise comparisons. The absence of significant heterogeneity in treatment effect across major patient subgroups does not support any choice of aromatase inhibitor based on differential prognostic prediction.

Our data are consistent with those from two large prospective trials[21,22] that did head-to-head comparisons of anastrozole and exemestane or letrozole, with anastrozole as the control group. In the MA.27 trial[21] in 7576 patients, no advantage for exemestane over anastrozole in the event-free-survival analysis was observed; however, there were differences in side-effects, with fewer reports of osteoporosis or osteopenia, hypertriglyceridaemia, vaginal bleeding, and hypercholesterolaemia in patients on exemestane than in those on anastrozole, and liver function abnormalities and rare episodes of atrial fibrillation being less frequent on anastrozole than on exemestane. In the FACE trial[22] in 4136 patients with metastatic axillary nodes, letrozole was not superior to anastrozole in terms of disease-free survival or overall survival, and no difference was found in terms of toxicity. Our data are also consistent with indirect comparisons reported in the EBCTCG meta-analysis,[15] in which the recurrence rate ratios or anastrozole, exemestane, and letrozole compared with tamoxifen were 0·71, 0·67, and 0·73, respectively, suggesting they were similarly effective. Few of the side-effects were significantly different between the three aromatase inhibitors in our study, which did not allow for definition of distinct patterns and are not useful to guide decisions in clinical practice.

This study has several strengths. First, the results are consistent with findings of the EBCTCG meta-analysis[15] and reinforce the clinical interpretation that aromatase inhibitors have minimal benefit over tamoxifen during the first 2 years of treatment. Second, to our knowledge, FATA-GIM3 is the only trial to compare upfront treatment with a switch strategy using anastrozole, and the first trial to directly compare the three aromatase inhibitors; thus, contributing to the knowledge base, which is currently limited to indirect comparisons of the EBCTCG meta-analysis and two head-to-head trials, one of which was limited to node-positive patients. Third, the findings are generalisable given that simple and inclusive eligibility criteria were used and that the trial was done in a setting highly similar to clinical practice. As expected given that this study was done more recently than the other trials discussed here, the patient population enrolled in FATA-GIM3 is slightly older and has a better prognostic profile in terms of pathological nodal status and tumour size than patients in the TEAM and BIG1-98

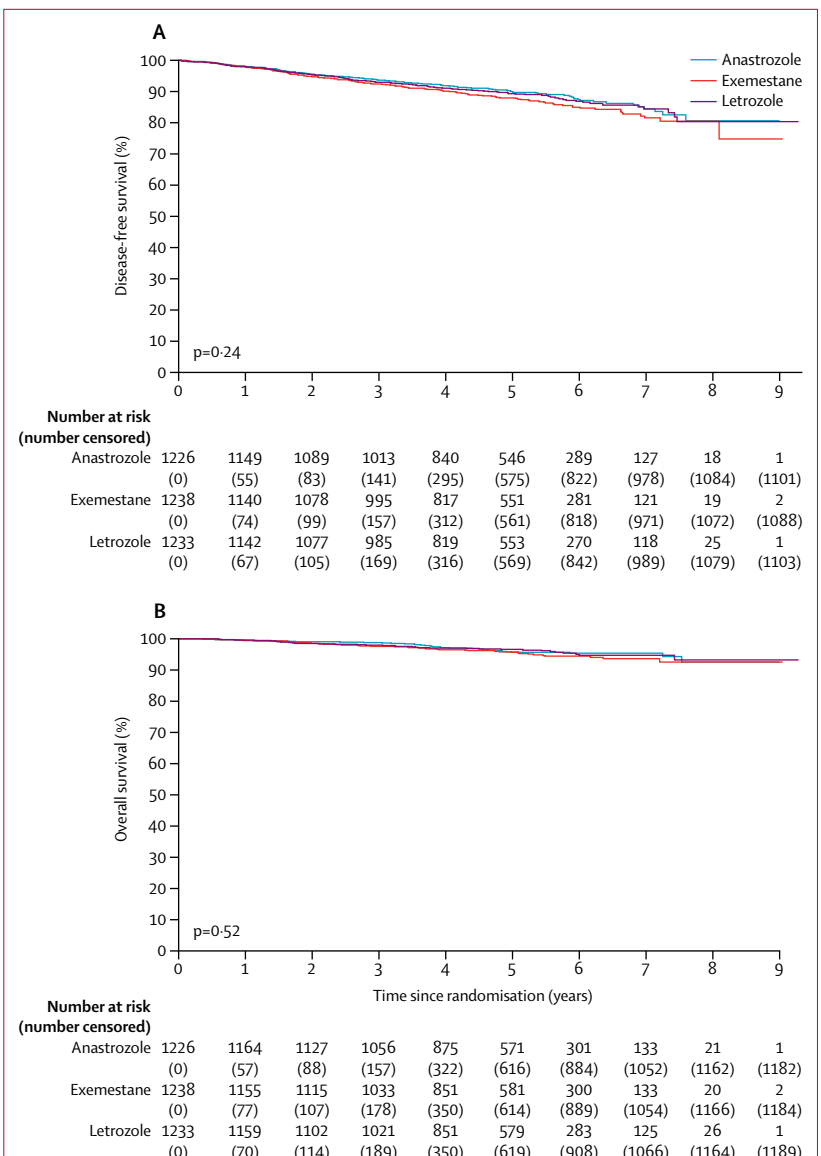

Figure 3: **Disease-free survival (A) and overall survival (B) according to aromatase inhibitor**

	Switch (n=1761)			Upfront (n=1766)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Cardiac arrhythmia	71 (4%)	7 (<1%)	0	77 (4%)	3 (<1%)	0
Supraventricular and nodal arrhythmia	33 (2%)	3 (<1%)	0	27 (2%)	2 (<1%)	0
Cardiac general	368 (21%)	16 (1%)	3 (<1%)	342 (19%)	20 (1%)	3 (<1%)
Ischaemia or infarction	6 (<1%)	1 (<1%)	1 (<1%)	8 (1%)	6 (<1%)	3 (<1%)
Hypertension	342 (19%)	11 (1%)	0	317 (18%)	12 (1%)	0
Constitutional	294 (17%)	4 (<1%)	0	283 (16%)	8 (1%)	0
Fatigue	178 (10%)	3 (<1%)	0	166 (9%)	5 (<1%)	0
Weight gain	89 (5%)	1 (<1%)	0	76 (4%)	2 (<1%)	0
Dermatology or skin	128 (7%)	4 (<1%)	0	90 (5%)	5 (<1%)	0
Pruritus	51 (3%)	2 (<1%)	0	33 (2%)	4 (<1%)	0
Dermatology, other	38 (2%)	1 (<1%)	0	33 (2%)	2 (<1%)	0
Endocrine (hot flushes)*	193 (11%)	0	0	145 (8%)	0	0
Gastrointestinal	190 (11%)	6 (<1%)	0	145 (8%)	8 (1%)	0
Constipation	51 (3%)	1 (<1%)	0	37 (2%)	0	0
Gastritis	40 (2%)	2 (<1%)	0	37 (2%)	2 (<1%)	0
Other	46 (3%)	1 (<1%)	0	36 (2%)	4 (<1%)	0
Lymphatics (oedema)	87 (5%)	1 (<1%)	0	66 (4%)	2 (<1%)	0
Metabolic or laboratory	1287 (73%)	23 (1%)	8 (1%)	1357 (77%)	23 (1%)	6 (<1%)
ALT or AST	53 (3%)	3 (<1%)	0	45 (3%)	3 (<1%)	0
Cholesterol†	1035 (59%)	2 (<1%)	3 (<1%)	1154 (65%)	4 (<1%)	5 (<1%)
Glucose	687 (39%)	17 (1%)	1 (<1%)	666 (38%)	14 (1%)	1 (<1%)
Triglyceride‡	543 (31%)	5 (<1%)	1 (<1%)	458 (26%)	2 (<1%)	0
Musculoskeletal†	745 (42%)	128 (7%)	2 (<1%)	924 (52%)	125 (7%)	3 (<1%)
Osteoporosis§	248 (14%)	95 (5%)	0	348 (20%)	74 (4%)	0
Arthritis†	429 (24%)	26 (1%)	1 (<1%)	557 (32%)	36 (2%)	2 (<1%)
Muscle weakness or pain§	225 (13%)	5 (<1%)	0	286 (16%)	8 (1%)	0
Bone pain†	373 (21%)	13 (1%)	1 (<1%)	458 (26%)	23 (1%)	2 (<1%)
Neurology	205 (12%)	11 (1%)	5 (<1%)	211 (12%)	13 (1%)	3 (<1%)
Depression	101 (6%)	4 (<1%)	0	81 (4%)	5 (<1%)	1 (<1%)
Anxiety	68 (4%)	2 (<1%)	0	55 (3%)	2 (<1%)	0
CNS cerebrovascular ischaemia	1 (<1%)	4 (<1%)	5 (<1%)	2 (<1%)	1 (<1%)	2 (<1%)
Other¶	47 (3%)	3 (<1%)	0	73 (4%)	6 (<1%)	0
Pain	59 (3%)	2 (<1%)	0	62 (4%)	0	0
Headache	33 (2%)	1 (<1%)	0	35 (2%)	0	0
Other	29 (2%)	1 (<1%)	0	33 (2%)	0	0
Pulmonary	28 (2%)	3 (<1%)	0	31 (2%)	5 (<1%)	0
Renal or genitourinary	22 (1%)	0	0	23 (1%)	4 (<1%)	0
Sexual or reproductive function†	52 (3%)	0	0	16 (1%)	0	0
Vaginal†	29 (2%)	0	0	6 (<1%)	0	0
Vascular‡	52 (3%)	14 (1%)	2 (<1%)	36 (2%)	5 (<1%)	0
Thrombosis or embolism	20 (1%)	9 (1%)	2 (<1%)	14 (1%)	3 (<1%)	0
Endometrium†	52 (3%)	8 (1%)	0	11 (1%)	1 (<1%)	0
Other event	67 (4%)	10 (1%)	0	66 (4%)	5 (<1%)	1 (<1%)

Data are n (%). Adverse events are reported if grade 1 or 2 adverse events occurred in ≥10% of patients, if grade 3 or 4 adverse events occurred in any patient, or if the difference between the groups was significant. The absence of a footnote indicates that the difference was not significant. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *p=0·005. †p<0·0001. ‡p=0·007. §p=0·003. ¶p=0·001.

Table 3: **Summary of adverse events by schedule**

studies.[17–19] Fourth, FATA-GIM3 was funded solely by academic support, thus enabling us to do a a three-drug comparison. Finally, centralised randomisation and intention-to-treat analyses preserved similarity of the comparison groups, and the proportions of patients lost to follow-up were low and similar among treatment groups, so that any selection bias seems unlikely.

The main limitation of this study was that the number of events, lower than planned, led to underpowered comparisons; the actual power of the analysis comparing the two schedules was reduced to 0·59. This reduction happened mainly because enrolment was slower than planned (accrual took 64 months instead of 36 months), while the observed 5-year disease-free survival in the switch group was only slightly less than assumed in the sample size definition (88·5% *vs* 90%). However, the proportion of patients who had a primary event was consistent with other relevant trials, both when considering events related to breast cancer (7·2% *vs* 6·1–10·4%[18,19,21]) and when considering non-breast malignancies (3·6% *vs* 3·1–4·5%[17,21]). The FACE trial,[22] which included only node-positive patients, reported a higher proportion of events (17·1%) than reported here. Furthermore, the first analysis of the TEAM trial[19] reported a larger proportion of breast cancer-related events than reported here (10·4% *vs* 7·2%). Moreover, the follow-up of FATA-GIM3 (60 months) is within the range of other studies (49–71 months);[18,19,21] TEAM[17] was the only trial to report a longer follow-up period (10 years). These similarities suggest that, even if comparisons in FATA-GIM3 were underpowered, analyses have been done at a reasonable time and with mature data.

Another possible study limitation is the fact that patients and physicians were not masked to treatment assignment; however, statistical analyses were done by individuals masked to treatment assignment and, thus, information bias should be minimal.

Follow-up procedures in FATA-GIM3 were more intensive than recommended in clinical practice guidelines. This decision was made to avoid a minimal follow-up strategy impeding the chance of finding a difference between the groups. Such an approach is consistent with the 2006 American Society of Clinical Oncology guidelines,[23] which state that follow-up procedures in clinical trials designed to compare or validate treatment approaches might be different from those indicated for clinical practice.

The relevance of FATA-GIM3 might be considered low, because its results are consistent with previous evidence and come after other publications addressing the same questions. However, relevance has to be judged at the time of the clinical trial design and not post hoc on the basis of the observed results. Otherwise, trials yielding negative results would be considered as non-relevant or of low relevance, exaggerating publication bias, inconsistent with best practice in clinical research.

	Anastrozole (n=1175)			Exemestane (n=1177)			Letrozole (n=1175)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Cardiac arrhythmia	56 (5%)	2 (<1%)	0	45 (4%)	5 (<1%)	0	47 (4%)	3 (<1%)	0
Supraventricular and nodal arrhythmia	29 (2%)	1 (<1%)	0	15 (1%)	3 (<1%)	0	16 (1%)	1 (<1%)	0
Cardiac general	246 (21%)	14 (1%)	3 (<1%)	227 (19%)	12 (1%)	2 (<1%)	237 (20%)	10 (1%)	1 (<1%)
Ischaemia or infarction	4 (<1%)	2 (<1%)	3 (<1%)	5 (<1%)	2 (<1%)	1 (<1%)	5 (<1%)	3 (<1%)	0
Hypertension	226 (19%)	10 (1%)	0	215 (18%)	8 (1%)	0	218 (19%)	5 (<1%)	0
Constitutional	200 (17%)	4 (<1%)	0	187 (16%)	5 (<1%)	0	190 (16%)	3 (<1%)	0
Fatigue	128 (11%)	3 (<1%)	0	106 (9%)	3 (<1%)	0	110 (9%)	2 (<1%)	0
Weight gain	47 (4%)	1 (<1%)	0	56 (5%)	2 (<1%)	0	62 (5%)	0	0
Dermatology or skin	65 (6%)	1 (<1%)	0	79 (7%)	3 (<1%)	0	74 (6%)	5 (<1%)	0
Pruritus	22 (2%)	1 (<1%)	0	30 (3%)	1 (<1%)	0	32 (3%)	4 (<1%)	0
Dermatology other	20 (2%)	0	0	32 (3%)	1 (<1%)	0	19 (2%)	2 (<1%)	0
Endocrine (hot flushes)	110 (9%)	0	0	126 (11%)	0	0	102 (9%)	0	0
Gastrointestinal*	113 (10%)	3 (<1%)	0	136 (12%)	8 (1%)	0	86 (7%)	3 (<1%)	0
Nausea	29 (2%)	0	0	36 (3%)	0	0	19 (2%)	0	0
Constipation	25 (2%)	0	0	40 (3%)	1 (<1%)	0	23 (2%)	0	0
Gastritis	29 (2%)	0	0	29 (2%)	3 (<1%)	0	19 (2%)	1 (<1%)	0
Other	28 (2%)	2 (<1%)	0	37 (3%)	2 (<1%)	0	17 (1%)	1 (<1%)	0
Lymphatics (oedema)	57 (5%)	0	0	47 (4%)	2 (<1%)	0	49 (4%)	1 (<1%)	0
Metabolic/laboratory†	904 (77%)	16 (1%)	3 (<1%)	852 (72%)	13 (1%)	3 (<1%)	888 (76%)	17 (1%)	8 (1%)
ALT or AST	33 (3%)	0	0	27 (2%)	4 (<1%)	0	38 (3%)	2 (<1%)	0
Cholesterol‡	749 (64%)	2 (<1%)	1 (<1%)	696 (59%)	1 (<1%)	1 (<1%)	744 (63%)	3 (<1%)	6 (1%)
Glucose	478 (41%)	16 (1%)	0	429 (36%)	7 (1%)	1 (<1%)	446 (38%)	8 (1%)	1 (<1%)
Triglyceride	342 (29%)	1 (<1%)	0	313 (27%)	2 (<1%)	0	346 (29%)	4 (<1%)	1 (<1%)
Musculoskeletal	558 (47%)	81 (7%)	1 (<1%)	563 (48%)	82 (7%)	2 (<1%)	548 (47%)	90 (8%)	2 (<1%)
Osteoporosis	201 (17%)	52 (4%)	0	196 (17%)	53 (5%)	0	199 (17%)	64 (5%)	0
Arthritis	330 (28%)	19 (2%)	0	331 (28%)	24 (2%)	2 (<1%)	325 (28%)	19 (2%)	1 (<1%)
Muscle weakness or pain	150 (13%)	6 (1%)	0	185 (16%)	1 (<1%)	0	176 (15%)	6 (1%)	0
Bone pain	271 (23%)	12 (1%)	1 (<1%)	278 (24%)	8 (1%)	0	282 (24%)	16 (1%)	2 (<1%)
Neurology	138 (11%)	8 (1%)	0	128 (11%)	8 (1%)	3 (<1%)	150 (13%)	8 (1%)	5 (<1%)
Depression	58 (5%)	3 (<1%)	0	60 (5%)	3 (<1%)	0	64 (5%)	3 (<1%)	1 (<1%)
Anxiety	43 (4%)	1 (<1%)	0	40 (3%)	2 (<1%)	0	40 (3%)	1 (<1%)	0
CNS cerebrovascular ischaemia	2 (<1%)	2 (<1%)	0	1 (<1%)	3 (<1%)	3 (<1%)	0	0	4 (<1%)
Other	40 (3%)	3 (<1%)	0	37 (3%)	2 (<1%)	0	43 (4%)	4 (<1%)	0
Pain	37 (3%)	1 (<1%)	0	40 (3%)	1 (<1%)	0	44 (4%)	0	0
Headache	26 (2%)	0	0	19 (2%)	1 (<1%)	0	23 (2%)	0	0
Other	15 (1%)	1 (<1%)	0	23 (2%)	0	0	24 (2%)	0	0
Pulmonary	23 (2%)	2 (<1%)	0	17 (1%)	3 (<1%)	0	19 (2%)	3 (<1%)	0
Renal or genitourinary	20 (2%)	3 (<1%)	0	10 (1%)	0	0	15 (1%)	1 (<1%)	0
Vascular	30 (3%)	6 (1%)	0	29 (2%)	5 (<1%)	1 (<1%)	29 (2%)	8 (1%)	1 (<1%)
Thrombosis or embolism	11 (1%)	5 (<1%)	0	10 (1%)	4 (<1%)	1 (<1%)	13 (1%)	3 (<1%)	1 (<1%)
Endometrium	10 (1%)	5 (<1%)	0	27 (2%)	1 (<1%)	0	26 (2%)	3 (<1%)	0
Other	41 (3%)	5 (<1%)	0	47 (4%)	6 (1%)	0	45 (4%)	4 (<1%)	1 (<1%)

Data are n (%). Adverse events are reported if grade 1 or 2 adverse events occurred in ≥10% of patients, if grade 3 or 4 adverse events occurred in any patient, or if the difference between the groups was significant. The absence of a footnote indicates that the difference was not significant. ALT=alanine aminotransferase. AST=aspartate aminotransferase. *p=0·0007 in three-drug comparison; p<0·0001 for exemestane *vs* letrozole. †p=0·002 in three-drug comparison; p=0·004 for exemestane *vs* anastrozole; p=0·002 for exemestane *vs* letrozole. ‡p=0·0004 in three-drug comparison; p=0·005 for exemestane *vs* anastrozole; p=0·001 for exemestane *vs* letrozole.

Table 4: **Summary of adverse events by aromatase inhibitor**

FATA-GIM3 was relevant at the time of its planning because the upfront strategy (with anastrozole) was about to become standard practice after the publication of the ATAC study,[3] despite indirect comparisons[11] suggesting that the switch strategy might be more effective than the upfront strategy, musculoskeletal and cardiac toxicity

being considered more probable with longer exposure to aromatase inhibitors, and the cost of upfront treatment being much higher than the cost of the switch strategy. Therefore, investigation of whether the strategy that was going to become standard practice in the absence of direct evidence was actually better than the strategy that might be more effective, less toxic, and less expensive was warranted. Our results are consistent with findings published in the past 10 years and fill some of the knowledge gaps (namely a comparison between the upfront and switch schedules when anastrozole is used, and a direct comparison of the three aromatase inhibitors in both node-negative and node-positive patients), providing direct evidence in a setting in which only indirect evidence has been available.

Finally, findings from FATA-GIM3, combined with those from the TEAM and BIG1-98 trials,[17–19] have implications for the affordability of adjuvant treatment for breast cancer worldwide. When the study was planned, the cost of 1 day of treatment with aromatase inhibitors in Italy was more than ten times higher than that with tamoxifen. In the USA, higher costs and copayments have been shown to lead to greater non-adherence to treatment with aromatase inhibitors and adherence has been improved by the increasing availability of generic drugs.[24] Nevertheless, even in countries where generic formulations are available, tamoxifen remains the cheapest drug and, because of the long duration of adjuvant treatment, a more affordable schedule might favour adherence in countries where, or in patients for whom, affordability is a concern.

The future direction of clinical research in the adjuvant hormonal treatment of breast cancer will inevitably relate to treatment duration, given that risk of relapse remains high even after 20 years of follow-up, at least for patients with poor prognostic factors.[25] Therefore, findings regarding the possibility of intermittent treatment provide new perspectives that might inform future clinical trials.[26,27]

In conclusion, the results of FATA-GIM3 and other available evidence suggest that there could be a small but not clinically significant advantage in using the upfront instead of the switch strategy in adjuvant hormonal treatment of postmenopausal patients with early breast cancer. Furthermore, there is no evidence that differences in efficacy exist among the three aromatase inhibitors. Therefore, the decision-making process when prescribing treatment for postmenopausal women with endocrine-sensitive breast cancer should take into account patient preference, tolerability, and financial constraints when the schedule and the aromatase inhibitor to include in the therapeutic plan are chosen.

Contributors

SDP, CG, and FP contributed to the study design and data analysis. SDP, CG, GA, and FP wrote the manuscript. All authors (apart from CG) contributed to data collection. All authors contributed to the data interpretation and approved the final manuscript.

Declaration of interests

SDP reports personal fees from Pfizer, AstraZeneca, and Novartis, during the conduct of the study, and grants from AstraZeneca, outside the submitted work. MDL reports personal fees from Novartis, Roche, AstraZeneca, Amgen, Celgene, Pfizer, and Eli Lilly, outside the submitted work. GA reports personal fees from Roche, GlaxoSmithKline, Amgen, Takeda, Ipsen, Novartis, Eli Lilly, Pfizer, and Celgene, outside the submitted work. LDM reports personal fees and non-financial support from Roche and Novartis, non-financial support from Celgene, and personal fees from Pfizer, Ipsen, Takeda, and Eli Lilly, outside the submitted work. FC reports personal fees from Amgen and Genomic Health, outside the submitted work. FM reports personal fees from AstraZeneca, Novartis, and Roche, outside the submitted work. FP reports grants from Italian Drug Agency (AIFA), during the conduct of the study, and personal fees from AstraZeneca, Eli Lilly, Roche, Bayer, Ipsen, and Bristol-Myers Squibb, outside the submitted work. All other authors declare no competing interests.

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