Anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, as adjuvant treatment of breast cancer. The FATA-GIM3 randomized phase III trial.

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Abstract

Background

Uncertainty exists on the schedule of adjuvant treatment of breast cancer with aromatase inhibitors (AIs); no trial has directly compared anastrozole versus exemestane versus letrozole. We tested superiority of upfront AIs versus tamoxifen then AIs (switch strategy) and compared the three AIs.

Methods

FATA-GIM3 is a multicenter, open label, 2x3 factorial phase 3 randomized trial of anastrozole (1 mg/die), exemestane (25 mg/die) or letrozole (2·5 mg/die) upfront for 5 years or tamoxifen (20 mg/die) for 2 years then AIs to year 5, in postmenopausal hormone-receptor positive early breast cancer patients. Randomization used a minimization procedure considering ER/PgR, HER-2, previous chemotherapy, and pathologic nodal status as strata. Disease-free survival (DFS - local or distant relapse, second breast or non-breast cancer, DCIS and death, whichever came first) was the primary end-point. The minimum advantage to declare superiority of upfront AIs vs switch was assumed equal to 2% at 5-year. Final primary analyses are reported, based on intention-to-treat. Follow-up is continuing to allow future secondary analyses. EUDRACT: 2006-004018-42. ClinicalTrials.gov: NCT00541086

Findings

From March 2007 to July 2012, 3697 patients were enrolled. After 5-year median follow-up, 401 events were reported, 211/1850 (11·4%) with switch and 190/1847 (10·3%) with upfront treatment. Five-year DFS was 88·5% (95%CI 86·7-90·0) with switch and 89·8%

(95%CI 88·2-91·2) with upfront (delta 1·3%, 95% CI -0·9 to 3·5; HR 0·89, 95%CI 0·73 to 1·08; P=0·23), and it was 90·0% (95%CI 87·9-91·7) with anastrozole, 88·0% (95%CI 85·8-89·9) with exemestane and 89·4% (95%CI 87·3-91·1) with letrozole (P=0·24). There were no suspected unexpected serious adverse reactions and no treatment-related deaths. Musculoskeletal side effects were the most frequent grade 3-4 events, reported in 130 (7·4%) of 1761 patients and 128 (7·3%) of 1766 patients with switch and upfront, respectively; such events, at grade 1, were more frequent with upfront (745 [42·3%] out of 1761 patients with switch versus 924 [52·3] out of 1766 patients with upfront). Grade 3-4 events were less frequent than 2% for all the other reported side-effects; grade 3-4 cardiac side-effects were reported in 19 (1·1%) out 1761 patients and 23 (1·3%) out of 1766 patients with switch and upfront, respectively.

Interpretation

In the FATA-GIM3 trial, 5-year treatment with AIs was not superior to 2 years tamoxifen followed by AIs. None of the three AIs was superior in terms of efficacy. Therefore, patient preferences, tolerability and eventual financial constraints should be considered for clinical decision making.

Funding

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Introduction

Tamoxifen has been for many years the adjuvant treatment of choice for postmenopausal women with hormone-responsive breast cancer; 5-years treatment reduces the risk of recurrence by 47% and the risk of death by 26%.(1) However, an increased incidence of endometrial cancer, thromboembolic disorders, hot flushes, mood disorders and vaginal symptoms have been reported as relevant side effects of tamoxifen.(1,2)

Three aromatase inhibitors (AI), either non-steroidal (anastrozole and letrozole) or steroidal (exemestane), have been shown to improve the efficacy of endocrine adjuvant treatment if used in place of or sequenced with tamoxifen. All AIs cause arthralgia, bone pain and osteoporosis.(3-9)

In 2006, when the FATA-GIM3 trial was planned, there was an intense debate as to whether AIs should be used upfront or after 2 years of tamoxifen. A possible positive benefit on disease free survival (DFS) during the first two years of treatment played in favour of the upfront option; conversely, indirect comparisons of trials testing the switch strategy versus trials testing the upfront strategy suggested a greater effect of the sequential strategy, because of a possible lower induction of drug-resistant phenotypes. As for side effects musculoskeletal and cardiac toxicity were considered more likely with longer exposure to AI, but, following the ATAC study, that was the first large trial published in this field, upfront strategy with anastrozole was going to become standard practice.(3) Simulations and modeling approaches reported conflicting results, although displaying relevant clinical and economical implications.(10,11) Further, there was uncertainty on whether there were differences among AIs either in terms of efficacy or side-effects because they had never been directly compared in a single trial.

Therefore, FATA-GIM3 was planned to test whether the upfront was more effective than the switch strategy and to directly compare for the first time anastrozole versus exemestane versus letrozole. The trial met requirements of the Italian Drug Agency for independent clinical trials planned to improve clinical practice and was funded by the Agency.

Methods

Study design

FATA-GIM3 is an academic multicenter, open label, 2x3 factorial phase 3 randomized study promoted by the "Dipartimento di Endocrinologia ed Oncologia Molecolare e Clinica", Università Federico II, Napoli, Italy, and conducted in public Italian institutions. The protocol was approved by the Ethical Committees at all the participating Institutions.

FATA-GIM3 was designed to address two main efficacy analyses: (1) comparing upfront versus switch schedules, with the latter considered as control arm according to study design, and (2) comparing the three AIs among themselves. Focus was on main effects rather than on interaction because in published literature there was no suggestion that schedule effect would change across AIs.

Patients

Postmenopausal women, no age limit, with histological diagnosis of invasive breast cancer completely removed by surgery, any pathologic tumor size and axillary nodal status according to the 2003 American Joint Committee on Cancer - AJCC staging system,(12) were eligible if they provided written informed consent. For women younger than 60, lack of menses for more than one year or FSH levels within the postmenopausal range were required. Women who had previously undergone bilateral oophorectomy were eligible. The primary tumor had to score positive for estrogen (ER) or progesterone (PgR) receptor (≥10% tumor cells positive by immunohistochemistry or ≥ 10 fmol/mg cytosol protein by ligand binding assay). Adjuvant and/or neoadjuvant chemotherapy, if given, had to be completed before enrolment. Patients with HER-2 positive tumors were eligible and trastuzumab should be prescribed according to the authorized schedule.

Patients were excluded in case of hormone replacement therapy either concurrent or assumed during the month before randomization, recurrent or metastatic disease discovered during baseline staging, previous treatment with tamoxifen, another malignancy (breast cancer or other 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 which would place the patient at unusual risk with the study drugs, and treatment with other experimental drugs either concurrent or during the month before randomization.

Randomisation and masking

Patients were equally allocated to one of the six study arms by centralized randomization at the web site of the GIM group (https://www.oncotech.org/gim/home/) with a computerized minimization procedure that used ER/PgR status (both positive, one positive and one negative, one positive and one unknown), HER-2 status (positive [3+ at immunohistochemistry or FISH-positive], negative, unknown), previous chemotherapy (none, adjuvant, neoadjuvant or both), and pathologic nodal status (pN0, pN1, pN2 or pN3) as stratification variables. This was an open-label trial and patients and clinical staff were aware of treatment. Statistical analysis was blinded.

Procedures

Anastrozole (1 mg tablets) or exemestane (25 mg tablets) or letrozole (2·5 mg tablets), were given once daily, for 5 years (upfront) or for 3 years following 2 years of treatment with tamoxifen (20 mg tablets once daily). All study drugs were included in the Italian national formulary and reimbursed by the National Health System. Treatment might 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, the following rules were suggested: (i)

patients definitively interrupting tamoxifen were shifted to the AI that had been assigned by randomization; (ii) patients interrupting AI could receive tamoxifen as alternative treatment, shift to a different AI being discouraged. Permanent discontinuation could occur according to investigator's clinical judgment, unacceptable toxicity, patient's choice or disease recurrence.

Locoregional radiotherapy, if indicated according to standard guidelines, could be given either before or after randomization, also concurrently with study drugs. Trastuzumab had to be prescribed to patients with HER-2 positive tumors according to accepted schedule and indication. Hormone replacement therapy was prohibited. Biphosphonates were not allowed to prevent osteoporosis but could be prescribed to treat osteoporosis, if indicated, according to current practice.

Baseline staging included physical examination, blood chemistry and ECG within 1 month before randomization, chest X-ray and liver US or CT scan within 3 months before randomization, mammography and bone scan within 1 year before randomization. During treatment, visits and blood chemistry were planned every 6 months up to 5 years after randomization, then yearly; chest X-ray and liver US or CT scan were planned every 6 months for 3 years, then yearly; ECG, mammography and bone scan were planned yearly. Gynecologic examination and measure of bone mineral density were left to the choice of investigators at participating centres but data were collected.

Outcomes

The primary study endpoint was disease free survival (DFS) defined as the time from randomization to the occurrence of the first among locoregional or distant recurrence, contralateral invasive breast cancer, ductal carcinoma in situ, second malignancy other than breast and death for any cause. Such definition corresponds to the DFS-DCIS

definition in the Standardized Definitions for Efficacy End Points (STEEP) system.(13) There was no central review. Secondary end-points reported in this paper include overall survival (OS), defined as the time from randomization to death from any cause, and toxicity, codified according to Common Terminology Criteria for Adverse Events (CTCAE) v.3·0. Toxicity was assessed at every visit, for 5 years. The other secondary efficacy end-points according to the STEEP system (i.e. IDFS, DDFS, DRFS, RFS, 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 higher number of events will have been recorded.

Statistical analysis

Sample size plan assumed that a 2% difference of DFS at 5 years was the minimum clinically worthwhile advantage required to declare the upfront strategy more effective than the switch one. At initial planning in July 2006, based on comparisons versus tamoxifen, expected 5-yr DFS with the switch strategy was estimated to be 85%, corresponding to a hazard ratio (HR) of 0·86; with 2-sided significance level of 0·05, power equal to 0·80 and one interim futility analysis, 1354 events were required and the enrolment of approximately 10,000 patients was planned. In 2009, following the presentation of long term data of the ABCSG trial 8 at the 2008 San Antonio meeting, the expected 5-yr DFS in the switch arm was increased to 90% (amendment 1, October 2009), and HR decreased to 0·79. With 2-sided significance level of 0·05, power equal to 0·80 and three interim futility analyses, a maximum of 669 events were required, and a sample size of 3600 patients was planned (EAST 5 software). Interim futility analyses were planned to reject the alternative hypothesis only, according to a beta-spending function with Pocock boundary. Applying the same parameters, 792 events were required for the log-rank comparison of the three AIs, according to the Ahnn and Anderson approach.(14) It was planned that the

comparison of AIs would have been first performed when the result of the primary comparison between schedules would have been available. The first futility interim analysis, performed on May 2015 with 318 events did not lead to the early stopping of the trial. In 2015, following the publication of the EBCTCG meta-analysis,(15) and the long time still required to reach the planned events, the Independent Data Monitoring Committee suggested to perform 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 definitive closure data defined yet.

All statistical analyses were based on the intention-to-treat (ITT) strategy and were performed blinded to the treatment arms. The ITT population for efficacy analysis was represented by all the randomized patients. The ITT population for safety analysis was represented by all the patients for whom at least one safety case report form had been completed.

The primary DFS analysis comparing schedules had to be done with a multivariable Cox model including stratification variables, AI drug and centre size (three categories according to tertiles of the number of patients enrolled) as covariates. Proportionality assumption was checked by entering a time-dependent covariate of treatment by log(time) interaction. First order interactions between treatment and covariates were tested by likelihood ratio test of two nested models with and without interaction; the effect of treatments were reported as HR and 95% CI for subgroup categories in a Forest plot. Such analyses were protocol-specified for stratification variables (ER/PgR status, HER-2 status, previous chemotherapy, and pathologic nodal status) and decided post-hoc for consistency with relevant literature or following the request of reviewers for age, type of menopause, BMI, tumor size, histologic grade, previous trastuzumab and previous radiotherapy.

As for the comparison of the three AIs, the global null hypothesis of treatment equivalence had to be first tested by the log-rank test; only in case of statistical significance at the 0·05 level, pairwise comparisons between AIs would be performed with Bonferroni-Holm adjustment.(16) For descriptive aims, HR and 95% CI were also calculated with a multivariable Cox model including stratification variables, schedule and centre categories as covariates, assuming anastrozole as reference group.

First-order interaction between schedule (two categories) and AI (three categories) was assessed by a likelihood ratio test between the two models with and without the two interaction covariates, following a reviewer's request.

DFS and OS curves were drawn with the Kaplan-Meier method.

As for toxicity analyses, for each patient and for each type of toxicity, the worst degree ever suffered was calculated and reported as the occurrence of either any toxicity (grade 1 or higher) or severe toxicity (grade 3-4). The whole toxicity distribution (i.e. all grades suffered) was used for statistical comparisons. In both comparisons of strategies and AIs, analyses were performed by the Kruskal-Wallis (K-W) nonparametric ANOVA with significance level set at 0·01. If the overall AI comparison was statistically significant, pairwise comparisons between AIs were done by K-W test using the Bonferroni-Holm adjustment; specifically, the three alpha levels for sequential testing were 0·0033, 0·005, 0·01.

Stata/MP 14.2 for Windows (StatCorp LLC, USA) was used for statistical analyses.

FATA-GIM3 was registered in two public trial registries, EUDRACT number 2006-004018-42 and ClinicalTrials.gov identifier NCT00541086.

Role of the funding source

The study was proposed by academic researchers and was conducted thanks to a grant of the Italian Drug Agency (AIFA - study code FARM5K3MEE). 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

From March 9th, 2007 to July 31st, 2012, 3697 patients were enrolled at 76 Italian centres (figure 1).

Baseline characteristics of patients are summarised in table 1 by comparison and webappendix (pages 2 to 6) by treatment arm, also including details of baseline metabolic profile, comorbidity and bone health status. Median age was 64 (IQR 58-71); the primary tumor was pT1 in 2586 (69·9%) of 3697 patients; axillary lymph nodes were pathologically negative in 2378 (64·3%) of 3697 patients; 330 (8·9%) of 3697 tumors were HER2-positive. Adjuvant or neoadjuvant chemotherapy had been given prior to randomization to 1415 (38·3%) of the patients. All baseline characteristics were well balanced among study arms.

At 60 months median follow-up (IQR 46-72), 401 DFS events were reported and 138 patients had died, 53 of whom without cancer; 85 patients were diagnosed a second non-breast cancer, 5 of whom following a breast cancer recurrence (table 2 and webappendix page 7). Breast cancer was the most frequent cause of death both with the switch treatment (55 [3·0%] out of 1850 patients) and with the upfront one (30 [1·6%] out of 1847 patients).

DFS curves by treatment arm are reported in webappendix page 8.

At 5 years, DFS was 88·5% (95% CI 86·7-90·0) with the switch schedule (211 events) and 89·8% (95% CI 88·2-91·2) with the upfront one (190 events), and HR equal to 0·89 (95% CI 0·73 to 1·08; P=0·23 – figure 2a). At 5 years, OS was 95·3% (95% CI 94·1-96·3) with the switch schedule (80 deaths) and 96·8% (95% CI 95·7-97·6) with the upfront one (58

deaths), percentage difference being equal to 1·5% (95% CI 0·1 to 2·9), and HR equal to 0·72, (95% CI 0·51 to 1·00; P=0·05 – figure 2b).

At 5 years, DFS was 90·0% (95% CI 87·9-91·7) with anastrozole (124 events), 88·0% (95% CI 85·8-89·9) with exemestane (148 events) and 89·4 (95% CI 87·3-91·1) with letrozole (129 events; P=0·24 – figure 3a). Since the overall comparison of AIs was not statistically significant, pairwise comparisons between AIs were not performed.

Interaction test between schedule and AI drug was not statistically significant (P=0·26). As reported in figure A3 online, HR for E vs A was 1·24 (95% CI 0·97-1·57) and for L vs A was 1·05 (0·82-1·35). At 5 years, OS was 95·9% (95% CI 94·4-97·0) with anastrozole (43 deaths), 95·7% (95% CI 94·2-96·8) with exemestane (52 deaths) and 96·6% (95% CI 95·3-97·6) with letrozole (43 deaths; P=0·52 – figure 3b).

There was no statistically significant interaction of treatment effect (HR of progression or death) and baseline patients' or tumor's characteristics in either main comparisons (switch versus upfront AIs, webappendix page 9 and among AIs, webappendix pages 10-11).

Median time on tamoxifen was 24 months (IQR 23-25), as expected; median time on treatment was similar among the three AIs (32 [IQR 28-36] to 35 [IQR 30-36] months in the switch and 54 [IQR 52-60] to 56 [IQR 53-60] months in the upfront arms, webappendix page 12). Toxicity was the major cause of treatment interruption before than planned (webappendix page 13) being more frequent with tamoxifen (overall 204 [11·0%] out of 1850 patients) than with aromatase inhibitors (93 [5·0%] out of 1850 patients in the switch group and 131 [7·1%] out of 1847 patients in the upfront group). Endometrial side effects were the prevalent reason for tamoxifen interruption (66 [3·6%] out of 1850 patients) while musculoskeletal side effects were the prevalent reason for aromatase inhibitors

interruption (53 [2·9%] out of 1850 patients in the switch group and 76 [4·1%] out of 1847 patients in the upfront group).

Toxicity data were not available for 170 (4·6%) of 3697 patients and the rate of missing data was similar across comparison arms. Details of toxicity data by treatment arm are reported in webappendix pages 14 to 19. There were no suspected unexpected serious adverse reactions and no treatment-related deaths. Tables 3 and 4 summarize toxicity data by compared groups, according to planned statistical significance rules. Musculoskeletal side effects (including osteoporosis, arthritis, muscle weakness, pain) were the most frequent grade 3-4 events, reported in 130 (7·4%) of 1761 patients and 128 (7·3%) of 1766 patients in the switch and upfront group, respectively; such events, were significantly different between switch and upfront treatment because of a higher rate of grade 1 events in the latter group (745 [42·3%] out of 1761 patients with switch versus 924 [52·3] out of 1766 patients with upfront). Grade 3-4 events were less frequent than 2% for all the other reported side-effects; grade 3-4 cardiac side-effects were reported in 19 (1·1%) out 1761 patients and 23 (1·3%) out of 1766 patients in the switch and upfront group, respectively. Overall, hot flushes, hypertriglyceridemia, vaginal, vascular and endometrial adverse events were more frequent with the switch schedule while hypercholesterolemia, and neurologic symptoms were more frequent with the upfront schedule. Bone fractures were reported in 81 (4·6%) out of 1761 patients and 64 (3·6%) out of 1766 patients in the switch and upfront schedule, respectively. In addition, gastrointestinal side-effects were more frequent with exemestane than with letrozole, and hypercholesterolemia was more frequent with anastrozole and letrozole as compared with exemestane.

Discussion

FATA-GIM3 is a large trial addressing two major questions, dealing with the schedule and the type of aromatase inhibitors to be used as adjuvant treatment of hormone-receptor positive breast cancer.

The first question was whether the upfront schedule (i.e. 5 years of AIs) was more effective than a switch schedule, where AIs are used after 2 years of tamoxifen. Our findings were not statistically significant, assuming a minimum clinically relevant difference of 5-yr DFS equal to 2%, and the absolute difference observed throughout the whole DFS curves never reached the 2% threshold, with a maximum of 1·6% after 2 years. In addition, there was no significant heterogeneity of schedule effect across major subgroups. The number of deaths and other breast-related events are still too few to allow reliable conclusions.

Two other direct comparisons of upfront versus switch strategy were published while FATA-GIM3 was ongoing, one with letrozole, the BIG-1 98 trial, and one with exemestane, the TEAM trial. (17-19) Both trials found no statistically significant difference between the two schedules, and concluded that the two strategies are both appropriate treatment options. The EBCTCG meta-analysis, however, containing these two trials plus another small Italian study, found that the DFS was statistically significantly different in favour of the upfront strategy, although with a very small absolute benefit, 1.1% at 5 years of follow-up-declining to 0·7% at 7 years, the HR being 0·90 (95%CI 0·81-0·99).(15) We argue that such absolute differences are not clinically relevant. Therefore, physicians might reasonably present 5 years of AI or 2 years of tamoxifen then AI up to 5 years as similarly effective strategies and discuss with the patients the toxicity profile as a possible driver of the choice. Our data, indeed, confirm that musculoskeletal symptoms are the most frequent side-effects of treatment, occurring in more than half of the patients, and are

consistently more frequent in the upfront schedule due to the longer exposure to AIs. The opportunity to include patient preference and tolerability of therapy in the decision making process has been also recently underlined by the 2017 St.Gallen panelists, given the overall modest differences between tamoxifen and AIs.(20)

As for the comparison among the AIs, FATA-GIM3 is, to our knowledge, the first trial directly comparing the three aromatase inhibitors, anastrozole, exemestane and letrozole among themselves as adjuvant treatment of hormone-receptor positive breast cancer. We actually found no statistically significant difference in the 3-arm comparisons and therefore did not proceed to formal head-to-head comparisons. Lack of significant heterogeneity of treatment effect across major subgroups does not support any choice based on differential prognostic prediction.

Our data are consistent with those coming from two large prospective trials that compared head-to-head exemestane vs anastrozole and letrozole vs anastrozole.(21, 22) These two trials tested superiority of the experimental treatment having anastrozole as control arm. In the MA·27 trial, with 7576 randomized to exemestane or anastrozole, there was no advantage with exemestane in the event-free survival analysis; however, there were differences in side effects with osteoporosis/osteopenia, hypertriglyceridemia, vaginal bleeding, and hypercholesterolemia being less frequent with exemestane and liver function abnormalities and rare episodes of atrial fibrillation being less frequent on anastrozole.(21) In the FACE trial, conducted with 4136 patients all with metastatic axillary nodes, letrozole was found not superior to anastrozole in terms of DFS and overall survival, and even no difference was found in terms of toxicity.(22) Finally, our data are also consistent with indirect comparisons reported in the EBCTCG Overview where anastrozole, exemestane and letrozole report a 0· 71, 0· 67 and 0· 73 rate ratio when compared with tamoxifen, thus suggesting to be similarly effective.(15) The few significant but slight differences in side-

effects among the three AIs observed in FATA-GIM3 do not allow defining distinct patterns and are not useful to guide decision in clinical practice.

We believe that the FATA-GIM3 has several strengths. First, results are consistent with findings of meta-analysis and further reinforce the clinical interpretation that the benefit of AIs over tamoxifen during the first two years is minimal. Second, it is the only trial that compares upfront vs switch strategies with anastrozole. Third, it is the first trial that directly compares the three AI, thus giving an important contribution to the knowledge, 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. Fourth, generalizability of findings is high given that simple and inclusive eligibility criteria were applied and that the trial was performed in a setting highly similar to clinical practice. Interestingly, as expected due to the fact that FATA-GIM3 study was conducted more recently than the other trials discussed above, the patient population enrolled in FATA-GIM3 is slightly older and has a better prognostic profile according to pathologic nodal status and tumor size than the TEAM and BIG1-98 studies. Fifth, FATA-GIM3 was fully independent, sponsored by the Italian Drug Agency, with no economical support from pharmaceutical industries. Finally, centralized randomization and intention-to-treat analyses preserved similarity of the compared groups, and the rates of patients lost to follow-up were low and similar among treatment arms , so that any selection bias seems unlikely.

Conversely, as a main limitation, we acknowledge 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 happened mainly because the enrolment rate was slower than planned (64 rather than 36 months), while the observed 5-yr DFS in the switch arm was only slightly less than that assumed in the sample size definition (88·5% and 90%, respectively). In any case, the rate of events at the primary analysis is comparable with the other relevant trials, considering events related to breast cancer

(7·2% versus a range going from 6·1% to 10·4%) and including death without cancer and second non-breast malignancies (3·6% versus a range going from 3·1% to 4·5%). Of course, FACE that included only node-positive patients was published with a larger rate of events.(22) further, we acknowledge that the first analysis of the TEAM was published with a relatively larger rate of BC related events (10.4% vs 7.2).(19) Also, the follow-up time of FATA-GIM3 (60 months) is again within the range of the other studies (from 49 to 71 months), TEAM being the only trial reporting a longer (10 years) follow-up time.(17) Such considerations sustain our belief that, even if comparisons in FATA-GIM3 are underpowered, analyses have been conducted at a reasonable time and with mature data.

Lack of blinding for patients and physicians represents another possible study limitation; however, statistical analyses were performed blinded to the knowledge of treatment code, thus information bias should be minimal.

A comment is also required regarding follow-up procedures applied in FATA-GIM3 that were more intensive than what actually planned in clinical practice guidelines. This choice was based on the opportunity to avoid that minimal follow-up rules might play against the chance of finding a difference between compared arms. Such approach is consistent with the 2006 ASCO guidelines stating that follow-up procedures in clinical trials designed to evaluate or validate treatment approaches may be different from those indicated for clinical practice.(23)

The relevance of FATA-GIM3 might be interpreted as low, because its results are consistent with previous evidence, and arrive after other publications dealing with the same questions. However, relevance has to be judged at the time of the clinical trial design and not *post-hoc*, based on the observed results. Otherwise, trials yielding negative result would be considered as non-relevant or low-relevant, exaggerating the publication bias, in contrast with best practice of clinical research. FATA-GIM3 was highly relevant at the time of its planning because (a) upfront strategy (with anastrozole) was going to

become standard practice following the ATAC publication but (b) indirect comparisons suggested that switch might be a more effective strategy, (c) musculoskeletal and cardiac toxicity were considered more probable with longer exposure to AI, and (d) the cost of upfront was much higher than the cost of switch strategy. Therefore, it was reasonable to perform a trial to test whether the strategy that was going to become standard practice in absence of direct evidence was actually better than the strategy that might be more effective, less toxic and less expensive. Fortunately, FATA-GIM3 results are consistent with findings published in recent years and fills the gap on some issues (namely the comparison between upfront and switch schedule when anastrozole is used and the direct comparison among the three aromatase inhibitors in both node-negative and node-positive patients), giving direct evidence where indirect interpretation was the only available type of knowledge.

Finally, FATA-GIM3 results, combined with those of TEAM and BIG1-98, are important for the affordability of the adjuvant treatment of breast cancer worldwide. When the study was planned, in Italy, the cost of one day of treatment with AIs was more than ten times higher than with tamoxifen. In the United States, it has been shown that higher the cost and the copayment higher the non-adherence rate to treatment with aromatase inhibitors, adherence having been improved by availability of generic drugs.(24) Nevertheless, even in countries where generic formulations are available, tamoxifen remains the cheapest drug, and, due to the long duration of adjuvant treatment, the less expensive schedule might favour adherence in countries or for patients for whom affordability is a concern.

Future direction of clinical research in the adjuvant hormonal treatment of breast cancer will inevitably deal with treatment duration, given that risk of relapse remains significant even after 20 years of follow-up, at least for patients with worse prognostic factors.(25) In

this direction, recent findings regarding the possibility of intermittent treatment open new perspectives that might inform future clinical trials.(26, 27)

In conclusion, based on FATA-GIM3 results and other available evidence, there is a small advantage in using the upfront instead of the switch strategy in adjuvant hormonal treatment of postmenopausal patients with early breast cancer, without significant clinical implications; further there is no evidence yet about efficacy differences among the three aromatase inhibitors. Therefore the decision making process should rely upon patient preferences, tolerability and eventual financial constraints when choosing the schedule and the aromatase inhibitor to include in the therapeutic plan.

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Authors' contribution

Study design and data analysis: SDP, CG, FP. Data interpretation and final approval of text: SDP, CG, MDL, GB, GA, MGS, FR, AR, LDM, AAC, FC, SG, JF, AF, DA, LL, LM, FM, CV, AB, VL, AG, GM, RL, AL, CM, SR, FN, PC, FP.. Data collection: SDP, MDL, GB, GA, MGS, FR, AR, LDM, AAC, FC, SG, JF, AF, DA, LL, LM, FM, CV, AB, VL, AG, GM, RL, AL, CM, SR, FN, PC, FP. Writing of the draft manuscript: SDP, CG, GA, FP.

Legend of figures

Figure 1. Study flow

Figure 2. Kaplan-Meier estimated curves of disease-free (2a. top graph) and overall (2b. bottom graph) survival according to schedule. Red=Upfront; blue=Switch.

Figure 3. Kaplan-Meier estimated curves of disease-free (3a. top graph) and overall (3b. bottom graph) survival according to aromatase inhibitor. Blue=Anastrozole, red=Exemestane, green=Letrozole.

Research in context

Evidence before this study

Meta-analyses and prospective trials of adjuvant endocrine treatment of postmenopausal breast cancer patients were searched in Pubmed. The evidence before this study is represented in (i) Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analyses on the efficacy of adjuvant treatment with tamoxifen and aromatase inhibitors; (ii) two international trials comparing switch versus upfront schedules, with letrozole (BIG1-98 study) and exemestane (TEAM study), the latter recently updated with 10yrs follow-up; (iii) two trials comparing head to head anastrozole versus exemestane (MA.27 study) or letrozole (the FACE trial dedicated to node positive patients). Nevertheless, the two questions of the FATA-GIM3 trial have not yet been adequately and defintely answered. In fact, regarding treatment strategy, there is no direct evidence available on the comparison of switch versus upfront schedules with the use of anastrozole; and, regarding the efficacy of the different aromatase inhibitors, there is no direct evidence available comparing exemestane with letrozole and, more largely, the three aromatase inhibitors among themselves.

Tamoxifen given for 5 years reduces the annual risk of recurrence by 47% and the risk of death by 26%. Aromatase inhibitors reduce annual recurrence rates by about 30% compared with tamoxifen, and an aromatase inhibitor given for 5 years reduces 10-year breast cancer mortality rates by about 15% compared with 5 years of tamoxifen. Tamoxifen followed by letrozole is similarly effective to letrozole alone (BIG1-98) and tamoxifen followed by exemestane is similarly effective to exemestane alone (TEAM). Exemestane for 5 years is not better than anastrozole for 5 years (MA.27) and letrozole for 5 years is not better than anastrozole for 5 years among node-positive patients (FACE).

There is no difference in the two head-to-head comparisons of anastrozole versus exemestane or letrozole.

Added value of this study

FATA-GIM3 adds a significant piece of information to the comparison of the upfront schedule (i.e. 5 years of AIs) with the switch schedule filling the gap of knowledge regarding such schedules when anastrozole is used. The sample size and the number of events in the EBCTCG meta-analysis (12799 and 1470, respectively) and in FATA-GIM3 (3697 and 401, respectively) witness that the latter will significantly contribute to the global evidence on such comparison. FATA-GIM3 is the first trial that compares the three aromatase inhibitors and provides prospective data on the comparison between exemestane and letrozole and between letrozole and anastrozole in node-negative patients..

Implications of all the available evidence

The available evidence shows that the absolute difference between 5 years aromatase inhibitors and 2 years tamoxifen then aromatase inhibitors for 3 years is small, under what we defined as a threshold of clinical relevance. Available data suggest that there is no evidence of different efficacy among the three aromatase inhibitors. Therefore, in the decision making process on adjuvant hormonal treatment of postmenopausal patients with early breast cancer, patient preferences, tolerability and eventual financial constraints should be considered to choose which schedule and which aromatase inhibitor to include in the therapeutic plan.

Declaration of interest statement

SDP reports personal fees from Pfizer, Astra Zeneca, Novartis, during the conduct of the study and grants from Astra Zeneca outside the submitted work; MDL reports personal fees from Novartis, Roche, Astra Zeneca, Amgen, Celgene, Pfizer, and Eli Lilly, outside the submitted work; GA reports personal fees from Roche, personal fees from GSK, personal fees from Amgen, personal fees from Takeda, personal fees from Ipsen, personal fees from Novartis, personal fees from Eli Lilly, personal fees from Pfizer, personal fees from Celgene, outside the submitted work; LDM reports personal fees and non-financial support from Roche, personal fees and non-financial support from Novartis, non-financial support from Celgene, personal fees from Pfizer, personal fees from Ipsen, personal fees from Takeda, personal fees from Eli Lilly, outside the submitted work; FC reports personal fees from Amgen and Genomic Health, outside the submitted work; FM reports personal fees from Astra Zeneca, personal fees from Novartis, personal fees from Roche, outside the submitted work; FP reports grants from Italian Drug Agency (AIFA), during the conduct of the study; personal fees from Astra Zeneca, personal fees from Eli Lilly, personal fees from Roche, personal fees from Bayer, personal fees from Ipsen, personal fees from Bristol Myers Squibb, outside the submitted work.

Table 1. Baseline characteristics of patients by comparison arm

	Schedule		Aromatase inhibitor		
	Switch N=1850	**Up-front** N=1847	**Anastrozole** N=1226	**Exemestane** N=1238	**Letrozole** N=1233
	n (%)	n (%)	n (%)	n (%)	n (%)
Age					
Median (IQR)	64 (58-70)	64 (57-70)	64 (58-70)	64 (58-70)	63 (58-71)
<60	556 (30·0)	596 (32·3)	391 (31·9)	365 (29·5)	396 (32·1)
60 - 69	768 (41·5)	742 (40·2)	504 (41·1)	523 (42·2)	483 (39·2)
70 +	526 (28·4)	509 (27·6)	331 (27·0)	350 (28·3)	354 (28·7)
Type of menopause					
Over 60 or oophorectomy	1309 (70·8)	1271 (68·8)	842 (68·7)	885 (71·5)	853 (69·2)
<60 and >1yr amenorrhea	398 (21·5)	432 (23·4)	296 (24·1)	248 (20·0)	286 (23·2)
<60·and <1yr amenorrhea*	75 (4·1)	69 (3·7)	47 (3·8)	45 (3·6)	52 (4·2)
<60· unknown amenorrhea	68 (3·7)	75 (4·1)	41 (3·3)	60 (4·8)	42 (3·4)
Body Mass Index					
Median (IQR)	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/Normal	503 (27·2)	528 (28·6)	326 (26·6)	366 (29·6)	339 (27·5)
Overweight	537 (29·0)	568 (30·8)	388 (31·6)	357 (28·8)	360 (29·2)
Obese	432 (23·4)	410 (22·2)	285 (23·2)	269 (21·7)	288 (23·4)
Unknown	378 (20·4)	341 (18·5)	227 (18·5)	246 (19·9)	246 (20·0)
Hormone receptors					
Both positive	1646 (89·0)	1642 (88·9)	1094 (89·2)	1099 (88·8)	1095 (88·8)
Only one positive	204 (11·0)	205 (11·1)	132 (10·8)	139 (11·2)	138 (11·2)
HER-2 status					
Negative	1663 (89·9)	1669 (90·4)	1105 (90·1)	1114 (90·0)	1113 (90·3)
Positive	168 (9·1)	162 (8·8)	107 (8·7)	114 (9·2)	109 (8·8)
Unknown	19 (1·0)	16 (0·9)	14 (1·1)	10 (0·8)	11 (0·9)
Pathologic nodal status					
pN0	1191 (64·4)	1187 (64·3)	788 (64·3)	799 (64·5)	791 (64·2)
pN1	465 (25·1)	463 (25·1)	311 (25·4)	308 (24·9)	309 (25·1)
pN2/pN3	194 (10·5)	197 (10·7)	127 (10·4)	131 (10·6)	133 (10·8)

Table 1 (continued). Baseline characteristics of patients by comparison arm

	Schedule		Aromatase inhibitor		
	Switch	**Up-front**	**Anastrozole**	**Exemestane**	**Letrozole**
	N=1850	N=1847	N=1226	N=1238	N=1233
	n (%)	n (%)	n (%)	n (%)	n (%)
Pathologic tumor category					
pT1	1299 (70·2)	1287 (69·7)	863 (70·4)	856 (69·1)	867 (70·3)
pT2	446 (24·1)	447 (24·2)	296 (24·1)	306 (24·7)	291 (23·6)
pT3/pT4	45 (2·4)	46 (2·5)	33 (2·7)	24 (2·0)	34 (2·8)
Unknown	60 (3·2)	67 (3·6)	34 (2·8)	52 (4·2)	41 (3·3)
Histologic grading					
Low	242 (13·1)	243 (13·2)	169 (13·8)	152 (12·3)	164 (13·3)
Intermediate	1060 (57·3)	1069 (57·9)	708 (57·7)	699 (56·5)	722 (58·6)
High	407 (22·0)	390 (21·1)	256 (20·9)	281 (22·7)	260 (21·1)
Unknown	141 (7·6)	145 (7·9)	93 (7·6)	106 (8·6)	87 (7·1)
Previous chemotherapy					
None	1138 (61·5)	1144 (61·9)	757 (61·7)	764 (61·7)	761 (61·7)
Adjuvant	665 (35·9)	658 (35·6)	438 (35·7)	444 (35·9)	441 (35·8)
Neoadjuvant	47 (2·5)	45 (2·4)	31 (2·5)	30 (2·4)	31 (2·5)
Trastuzumab					
No	1660 (89·7)	1663 (90·0)	1107 (90·3)	1100 (88·9)	1116 (90·5)
Yes	131 (7·1)	126 (6·8)	88 (7·2)	88 (7·1)	81 (6·6)
Unknown	59 (3·2)	58 (3·1)	31 (2·5)	50 (4·0)	36 (2·9)
Radiotherapy					
No	544 (29·4)	536 (29·0)	394 (32·1)	334 (27·0)	352 (28·5)
Yes	1247 (67·4)	1253 (67·8)	801 (65·3)	854 (69·0)	845 (68·5)
Unknown	59 (3·2)	58 (3·1)	31 (2·5)	50 (4·0)	36 (2·9)

* postmenopausal FSH levels

Table 2. Distribution of events by comparison arm

	Schedule		Aromatase inhibitor		
	Switch	**Up-front**	**Anastrozole**	**Exemestane**	**Letrozole**
	N=1850	N=1847	N=1226	N=1238	N=1233
	n (%)	n (%)	n (%)	n (%)	n (%)
DFS events	211	190	124	148	129
Type of first DFS event					
Locoregional	30 (14·2)	26 (13·7)	12 (9·7)	30 (20·3)	14 (10·9)
Distant	99 (46·9)	84 (44·2)	63 (50·8)	57 (38·5)	63 (48·8)
Second breast cancer	13 (6·2)	16 (8·4)	12 (9·7)	11 (7·4)	6 (4·7)
Second non-breast cancer	44 (20·9)	36 (18·9)	26 (21·0)	29 (19·6)	25 (19·4)
Death without any cancer	25 (11·8)	28 (14·7)	11 (8·9)	21 (14·2)	21 (16·3)
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
Hematologic	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 3. Summary of toxicity by CTCAE grade and compared schedules

	Switch (N=1761)						Upfront (N=1766)					
	Grade 1-2		Grade 3		Grade 4		Grade 1-2		Grade 3		Grade 4	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
CARDIAC ARRHYTHMIA	71	(4·0)	7	(0·4)	0	(0·0)	77	(4·4)	3	(0·2)	0	(0·0)
Supraventricular and nodal arrhythmia	33	(1·9)	3	(0·2)	0	(0·0)	27	(1·5)	2	(0·1)	0	(0·0)
CARDIAC_GENERAL	368	(20·9)	16	(0·9)	3	(0·2)	342	(19·4)	20	(1·1)	3	(0·2)
Ischemia/infarction	6	(0·3)	1	(0·1)	1	(0·1)	8	(0·5)	6	(0·3)	3	(0·2)
Hypertension	342	(19·4)	11	(0·6)	0	(0·0)	317	(18·0)	12	(0·7)	0	(0·0)
CONSTITUTIONAL	294	(16·7)	4	(0·2)	0	(0·0)	283	(16·0)	8	(0·5)	0	(0·0)
Fatigue	178	(10·1)	3	(0·2)	0	(0·0)	166	(9·4)	5	(0·3)	0	(0·0)
Weight gain	89	(5·1)	1	(0·1)	0	(0·0)	76	(4·3)	2	(0·1)	0	(0·0)
DERMATOLOGY/SKIN	128	(7·3)	4	(0·2)	0	(0·0)	90	(5,1)	5	(0,3)	0	(0,0)
Pruritus	51	(2·9)	2	(0·1)	0	(0·0)	33	(1·9)	4	(0·2)	0	(0·0)
Dermatology other	38	(2·2)	1	(0·1)	0	(0·0)	33	(1·9)	2	(0·1)	0	(0·0)
ENDOCRINE Hot flushes [d]	193	(11·0)	0	(0·0)	0	(0·0)	145	(8·2)	0	(0·0)	0	(0·0)
GASTROINTESTINAL	190	(10·8)	6	(0·3)	0	(0·0)	145	(8·2)	8	(0·5)	0	(0·0)
Constipation	51	(2·9)	1	(0·1)	0	(0·0)	37	(2·1)	0	(0·0)	0	(0·0)
Gastritis	40	(2·3)	2	(0·1)	0	(0·0)	37	(2·1)	2	(0·1)	0	(0·0)
Gastrointestinal other	46	(2·6)	1	(0·1)	0	(0·0)	36	(2·0)	4	(0·2)	0	(0·0)
LYMPHATICS edema	87	(4·9)	1	(0·1)	0	(0·0)	66	(3·7)	2	(0·1)	0	(0·0)
METABOLIC/LABORATORY	1287	(73·1)	23	(1·3)	8	(0·5)	1357	(76·8)	23	(1·3)	6	(0·3)
ALT/AST	53	(3·0)	3	(0·2)	0	(0·0)	45	(2·5)	3	(0·2)	0	(0·0)
Cholesterol [a]	1035	(58·8)	2	(0·1)	3	(0·2)	1154	(65·3)	4	(0·2)	5	(0·3)
Glucose	687	(39·0)	17	(1·0)	1	(0·1)	666	(37·7)	14	(0·8)	1	(0·1)
Triglyceride [e]	543	(30·8)	5	(0·3)	1	(0·1)	458	(25·9)	2	(0·1)	0	(0·0)
MUSCULOSKELETAL [a]	745	(42·3)	128	(7·3)	2	(0·1)	924	(52·3)	125	(7·1)	3	(0·2)
Osteoporosis [c]	248	(14·1)	95	(5·4)	0	(0·0)	348	(19·7)	74	(4·2)	0	(0·0)
Arthritis [a]	429	(24·4)	26	(1·5)	1	(0·1)	557	(31·5)	36	(2·0)	2	(0·1)

Muscle weakness/pain [c]	225	(12·8)	5	(0·3)	0	(0·0)	286	(16·2)	8	(0·5)	0	(0·0)
Bone pain [a]	373	(21·2)	13	(0·7)	1	(0·1)	458	(25·9)	23	(1·3)	2	(0·1)
NEUROLOGY	205	(11·6)	11	(0·6)	5	(0·3)	211	(11·9)	13	(0·7)	3	(0·2)
Depression	101	(5·7)	4	(0·2)	0	(0·0)	81	(4·6)	5	(0·3)	1	(0·1)
Anxiety	68	(3·9)	2	(0·1)	0	(0·0)	55	(3·1)	2	(0·1)	0	(0·0)
CNS cerebrovascular ischemia	1	(0·1)	4	(0·2)	5	(0·3)	2	(0·1)	1	(0·1)	2	(0·1)
Neurology other [b]	47	(2·7)	3	(0·2)	0	(0·0)	73	(4·1)	6	(0·3)	0	(0·0)
PAIN	59	(3·4)	2	(0·1)	0	(0·0)	62	(3·5)	0	(0·0)	0	(0·0)
Headache	33	(1·9)	1	(0·1)	0	(0·0)	35	(2·0)	0	(0·0)	0	(0·0)
Pain other	29	(1·6)	1	(0·1)	0	(0·0)	33	(1·9)	0	(0·0)	0	(0·0)
PULMONARY	28	(1·6)	3	(0·2)	0	(0·0)	31	(1·8)	5	(0·3)	0	(0·0)
RENAL/GENITOURINARY	22	(1·2)	0	(0·0)	0	(0·0)	23	(1·3)	4	(0·2)	0	(0·0)
SEXUAL/REPRODUCTIVE FUNCTION [a]	52	(3·0)	0	(0·0)	0	(0·0)	16	(0·9)	0	(0·0)	0	(0·0)
Vaginal [a]	29	(1·6)	0	(0·0)	0	(0·0)	6	(0·3)	0	(0·0)	0	(0·0)
VASCULAR [e]	52	(3·0)	14	(0·8)	2	(0·1)	36	(2·0)	5	(0·3)	0	(0·0)
Thrombosis/Embolism	20	(1·1)	9	(0·5)	2	(0·1)	14	(0·8)	3	(0·2)	0	(0·0)
Endometrium [a]	52	(3·0)	8	(0·5)	0	(0·0)	11	(0·6)	1	(0·1)	0	(0·0)
Other event	67	(3·8)	10	(0·6)	0	(0·0)	66	(3·7)	5	(0·3)	1	(0·1)

Adverse events are reported if grade 1 or 2 occurred in ≥10% of patients, or if grade 3 or 4 occurred, or if the difference between compared groups was statistically significant. CTCAE categories are reported as uppercase, subcategories as lowercase.

P values were calculated by Kruskal Wallis non parametric ANOVA using the distribution of all grades of toxicity (see methods).

[a] P<0·0001, [b] P =0·001, [c] P =0·003, [d] P =0·005, [e] P =0·007.

Table 4. Summary of toxicity by CTCAE grade and compared aromatase inhibitors

	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**
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
CARDIAC ARRHYTHMIA	56 (4·8)	2 (0·2)	0 (0·0)	45 (3·8)	5 (0·4)	0 (0·0)	47 (4·0)	3 (0·3)	0 (0·0)
Supraventricular and nodal arrhythmia	29 (2·5)	1 (0·1)	0 (0·0)	15 (1·3)	3 (0·3)	0 (0·0)	16 (1·4)	1 (0·1)	0 (0·0)
CARDIAC_GENERAL	246 (20·9)	14 (1·2)	3 (0·3)	227 (19·3)	12 (1·0)	2 (0·2)	237 (20·2)	10 (0·9)	1 (0·1)
Ischemia/infarction	4 (0·3)	2 (0·2)	3 (0·3)	5 (0·4)	2 (0·2)	1 (0·1)	5 (0·4)	3 (0·3)	0 (0·0)
Hypertension	226 (19·2)	10 (0·9)	0 (0·0)	215 (18·3)	8 (0·7)	0 (0·0)	218 (18·6)	5 (0·4)	0 (0·0)
CONSTITUTIONAL	200 (17·0)	4 (0·3)	0 (0·0)	187 (15·9)	5 (0·4)	0 (0·0)	190 (16·2)	3 (0·3)	0 (0·0)
Fatigue	128 (10·9)	3 (0·3)	0 (0·0)	106 (9·0)	3 (0·3)	0 (0·0)	110 (9·4)	2 (0·2)	0 (0·0)
Weight gain	47 (4·0)	1 (0·1)	0 (0·0)	56 (4·8)	2 (0·2)	0 (0·0)	62 (5·3)	0 (0·0)	0 (0·0)
DERMATOLOGY/SKIN	65 (5·5)	1 (0·1)	0 (0·0)	79 (6·7)	3 (0·3)	0 (0·0)	74 (6·3)	5 (0·4)	0 (0·0)
Pruritus	22 (1·9)	1 (0·1)	0 (0·0)	30 (2·5)	1 (0·1)	0 (0·0)	32 (2·7)	4 (0·3)	0 (0·0)
Dermatology other	20 (1·7)	0 (0·0)	0 (0·0)	32 (2·7)	1 (0·1)	0 (0·0)	19 (1·6)	2 (0·2)	0 (0·0)
ENDOCRINE Hot flushes	110 (9·4)	0 (0·0)	0 (0·0)	126 (10·7)	0 (0·0)	0 (0·0)	102 (8·7)	0 (0·0)	0 (0·0)
GASTROINTESTINAL [a]	113 (9·6)	3 (0·3)	0 (0·0)	136 (11·6)	8 (0·7)	0 (0·0)	86 (7·3)	3 (0·3)	0 (0·0)
Nausea	29 (2·5)	0 (0·0)	0 (0·0)	36 (3·1)	0 (0·0)	0 (0·0)	19 (1·6)	0 (0·0)	0 (0·0)
Constipation	25 (2·1)	0 (0·0)	0 (0·0)	40 (3·4)	1 (0·1)	0 (0·0)	23 (2·0)	0 (0·0)	0 (0·0)
Gastritis	29 (2·5)	0 (0·0)	0 (0·0)	29 (2·5)	3 (0·3)	0 (0·0)	19 (1·6)	1 (0·1)	0 (0·0)
Gastrointestinal other	28 (2·4)	2 (0·2)	0 (0·0)	37 (3·1)	2 (0·2)	0 (0·0)	17 (1·4)	1 (0·1)	0 (0·0)
LYMPHATICS edema	57 (4·9)	0 (0·0)	0 (0·0)	47 (4·0)	2 (0·2)	0 (0·0)	49 (4·2)	1 (0·1)	0 (0·0)
METABOLIC/LABORATORY [b]	904 (76·9)	16 (1·4)	3 (0·3)	852 (72·4)	13 (1·1)	3 (0·3)	888 (75·6)	17 (1·4)	8 (0·7)
ALT/AST	33 (2·8)	0 (0·0)	0 (0·0)	27 (2·3)	4 (0·3)	0 (0·0)	38 (3·2)	2 (0·2)	0 (0·0)
Cholesterol [c]	749 (63·7)	2 (0·2)	1 (0·1)	696 (59·1)	1 (0·1)	1 (0·1)	744 (63·3)	3 (0·3)	6 (0·5)
Glucose	478 (40·7)	16 (1·4)	0 (0·0)	429 (36·4)	7 (0·6)	1 (0·1)	446 (38·0)	8 (0·7)	1 (0·1)
Triglyceride	342 (29·1)	1 (0·1)	0 (0·0)	313 (26·6)	2 (0·2)	0 (0·0)	346 (29·4)	4 (0·3)	1 (0·1)
MUSCULOSKELETAL	558 (47·5)	81 (6·9)	1 (0·1)	563 (47·8)	82 (7·0)	2 (0·2)	548 (46·6)	90 (7·7)	2 (0·2)
Osteoporosis	201 (17·1)	52 (4·4)	0 (0·0)	196 (16·7)	53 (4·5)	0 (0·0)	199 (16·9)	64 (5·4)	0 (0·0)

Arthritis	330 (28·1)	19 (1·6)	0 (0·0)	331 (28·1)	24 (2·0)	2 (0·2)	325 (27·7)	19 (1·6)	1 (0·1)
Muscle weakness/pain	150 (12·8)	6 (0·5)	0 (0·0)	185 (15·7)	1 (0·1)	0 (0·0)	176 (15·0)	6 (0·5)	0 (0·0)
Bone pain	271 (23·1)	12 (1·0)	1 (0·1)	278 (23·6)	8 (0·7)	0 (0·0)	282 (24·0)	16 (1·4)	2 (0·2)
NEUROLOGY	138 (11·7)	8 (0·7)	0 (0·0)	128 (10·9)	8 (0·7)	3 (0·3)	150 (12·8)	8 (0·7)	5 (0·4)
Depression	58 (4·9)	3 (0·3)	0 (0·0)	60 (5·1)	3 (0·3)	0 (0·0)	64 (5·4)	3 (0·3)	1 (0·1)
Anxiety	43 (3·7)	1 (0·1)	0 (0·0)	40 (3·4)	2 (0·2)	0 (0·0)	40 (3·4)	1 (0·1)	0 (0·0)
CNS cerebrovascular ischemia	2 (0·2)	2 (0·2)	0 (0·0)	1 (0·1)	3 (0·3)	3 (0·3)	0 (0·0)	0 (0·0)	4 (0·3)
Neurology other	40 (3·4)	3 (0·3)	0 (0·0)	37 (3·1)	2 (0·2)	0 (0·0)	43 (3·7)	4 (0·3)	0 (0·0)
PAIN	37 (3·1)	1 (0·1)	0 (0·0)	40 (3·4)	1 (0·1)	0 (0·0)	44 (3·7)	0 (0·0)	0 (0·0)
Headache	26 (2·2)	0 (0·0)	0 (0·0)	19 (1·6)	1 (0·1)	0 (0·0)	23 (2·0)	0 (0·0)	0 (0·0)
Pain other	15 (1·3)	1 (0·1)	0 (0·0)	23 (2·0)	0 (0·0)	0 (0·0)	24 (2·0)	0 (0·0)	0 (0·0)
PULMONARY	23 (2·0)	2 (0·2)	0 (0·0)	17 (1·4)	3 (0·3)	0 (0·0)	19 (1·6)	3 (0·3)	0 (0·0)
RENAL/GENITOURINARY	20 (1·7)	3 (0·3)	0 (0·0)	10 (0·8)	0 (0·0)	0 (0·0)	15 (1·3)	1 (0·1)	0 (0·0)
VASCULAR	30 (2·6)	6 (0·5)	0 (0·0)	29 (2·5)	5 (0·4)	1 (0·1)	29 (2·5)	8 (0·7)	1 (0·1)
Thrombosis/Embolism	11 (0·9)	5 (0·4)	0 (0·0)	10 (0·8)	4 (0·3)	1 (0·1)	13 (1·1)	3 (0·3)	1 (0·1)
Endometrium	10 (0·9)	5 (0·4)	0 (0·0)	27 (2·3)	1 (0·1)	0 (0·0)	26 (2·2)	3 (0·3)	0 (0·0)
Other event	41 (3·5)	5 (0·4)	0 (0·0)	47 (4·0)	6 (0·5)	0 (0·0)	45 (3·8)	4 (0·3)	1 (0·1)

Adverse events are reported if grade 1 or 2 occurred in ≥10% of patients, or if grade 3 or 4 occurred, or if the difference between compared groups was statistically significant. CTCAE categories are reported as uppercase, subcategories as lowercase.

P values were calculated by Kruskal Wallis non parametric ANOVA using the distribution of all grades of toxicity (see methods).

[a] 3-drug comparison: P=0·0007; exemestane vs letrozole: P<0·0001

[b] 3-drug comparison: P=0·002; exemestane vs anastrozole: P=0·004; exemestane vs letrozole: P=0·002

[c] 3-drug comparison: P=0·0004; exemestane vs anastrozole: P=0·005; exemestane vs letrozole: P=0·001

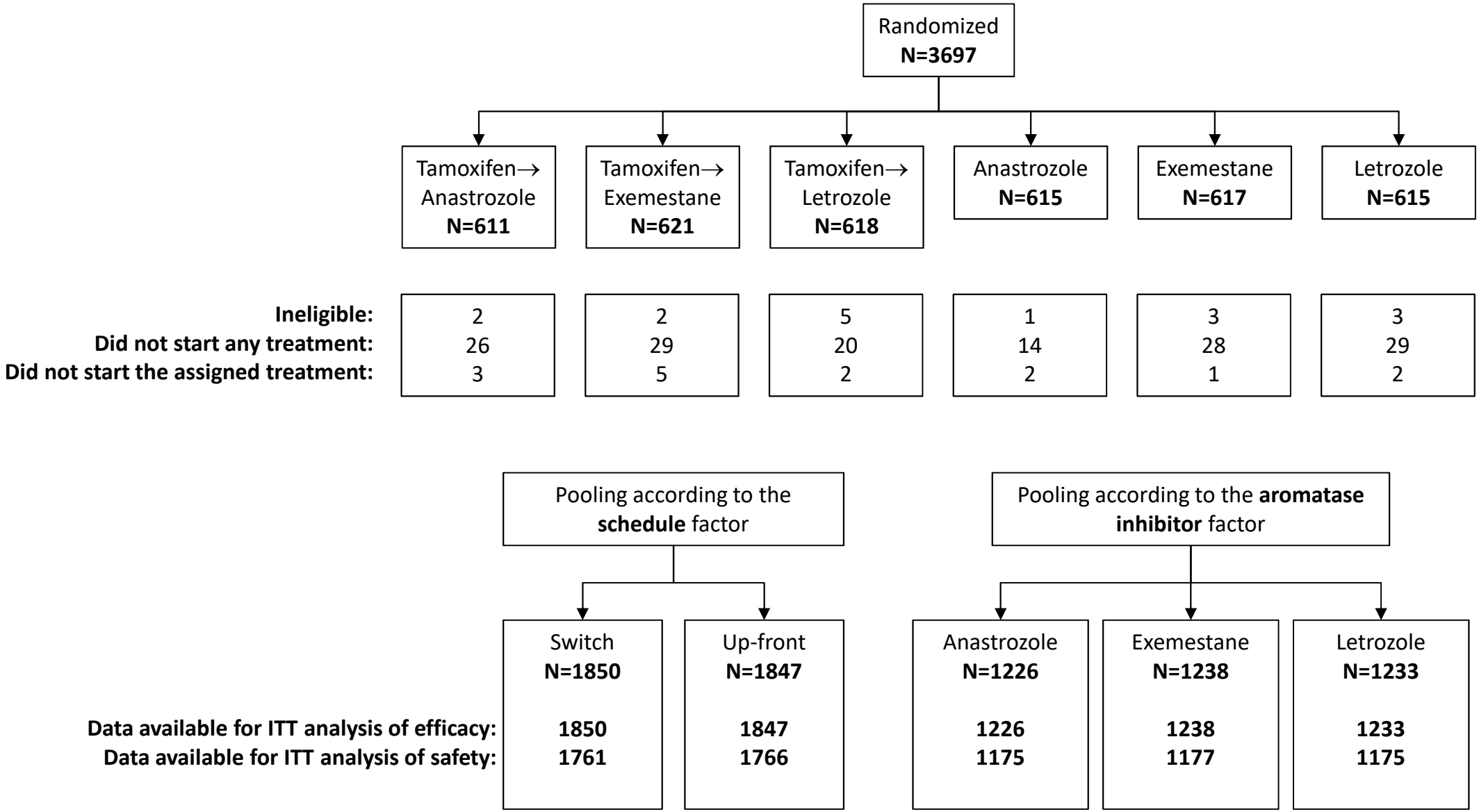
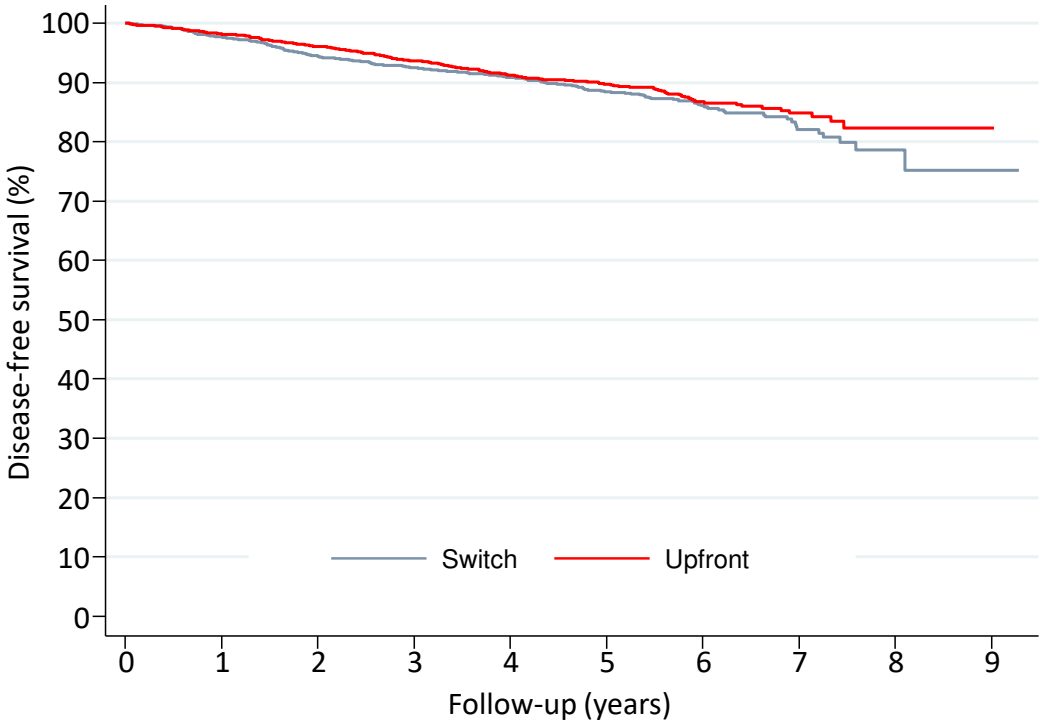

Randomized
N=3697
Tamoxifen→ Anastrozole N=611
Tamoxifen→ Exemestane N=621
Tamoxifen→ Letrozole N=618
Anastrozole N=615
Exemestane N=617
Letrozole N=615
Ineligible:
Did not start any treatment:
Did not start the assigned treatment:
2
26
3
2
29
5
5
20
2
1
14
2
3
28
1
3
29
2
Pooling according to the schedule factor
Pooling according to the aromatase inhibitor factor
Switch N=1850
Up-front N=1847
Anastrozole N=1226
Exemestane N=1238
Letrozole N=1233
Data available for ITT analysis of efficacy:
Data available for ITT analysis of safety:
1850
1761
1847
1766
1226
1175
1238
1177
1233
1175

Figure 1

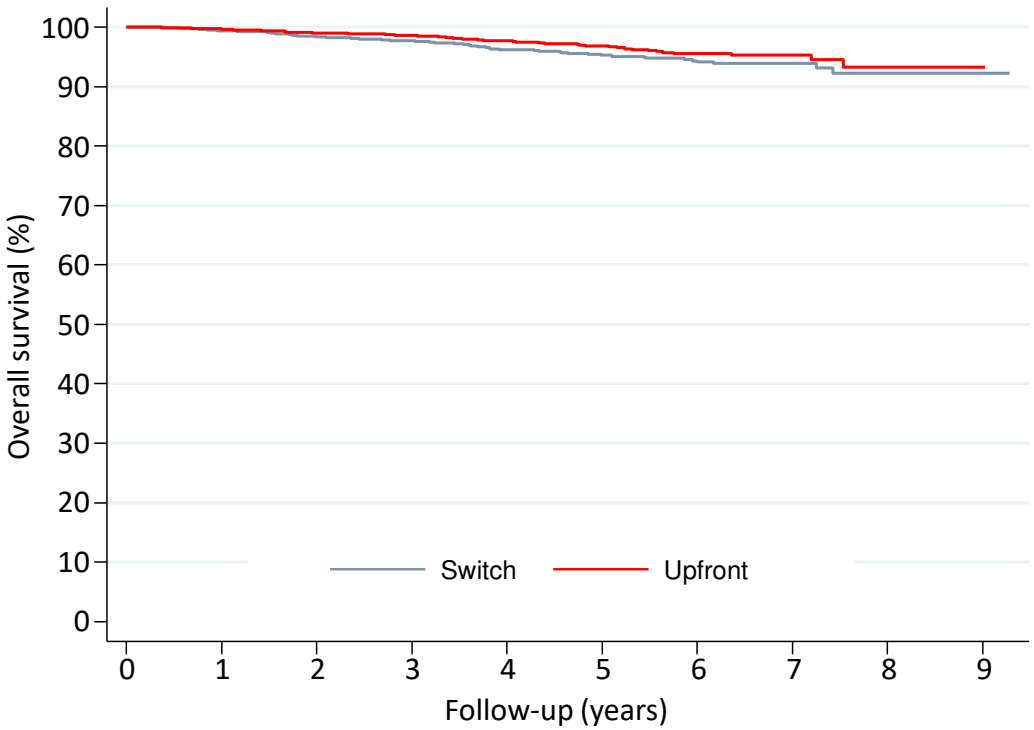
Figure 2a



Number at risk (number censored)

Switch	1850 (0)	1710 (100)	1611 (142)	1482 (239)	1225 (472)	813 (857)	407 (1249)	184 (1460)	34 (1606)	3 (1636)
Upfront	1847 (0)	1721 (96)	1633 (145)	1511 (228)	1251 (451)	837 (848)	433 (1233)	182 (1478)	28 (1629)	1 (1656)

Figure 2b

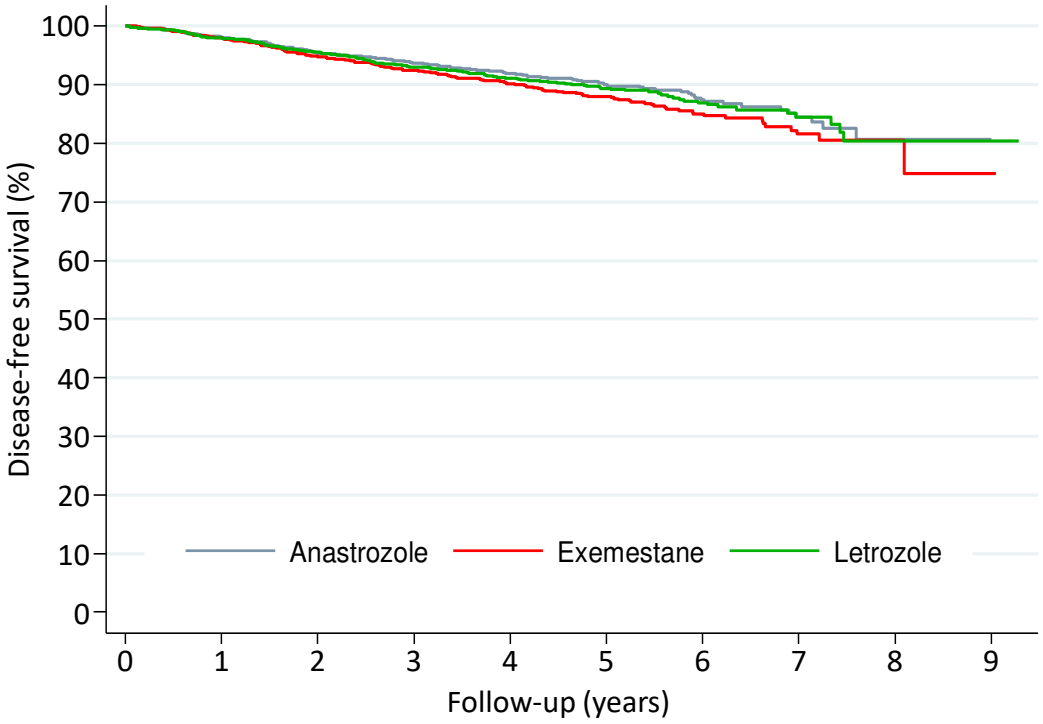


Number at risk (number censored)

Switch	1850 (0)	1737 (103)	1670 (153)	1548 (263)	1272 (517)	858 (922)	432 (1341)	199 (1573)	38 (1732)	3 (1767)
Upfront	1847 (0)	1741 (101)	1674 (156)	1562 (261)	1305 (505)	873 (927)	452 (1340)	192 (1599)	29 (1760)	1 (1788)

Figure 2

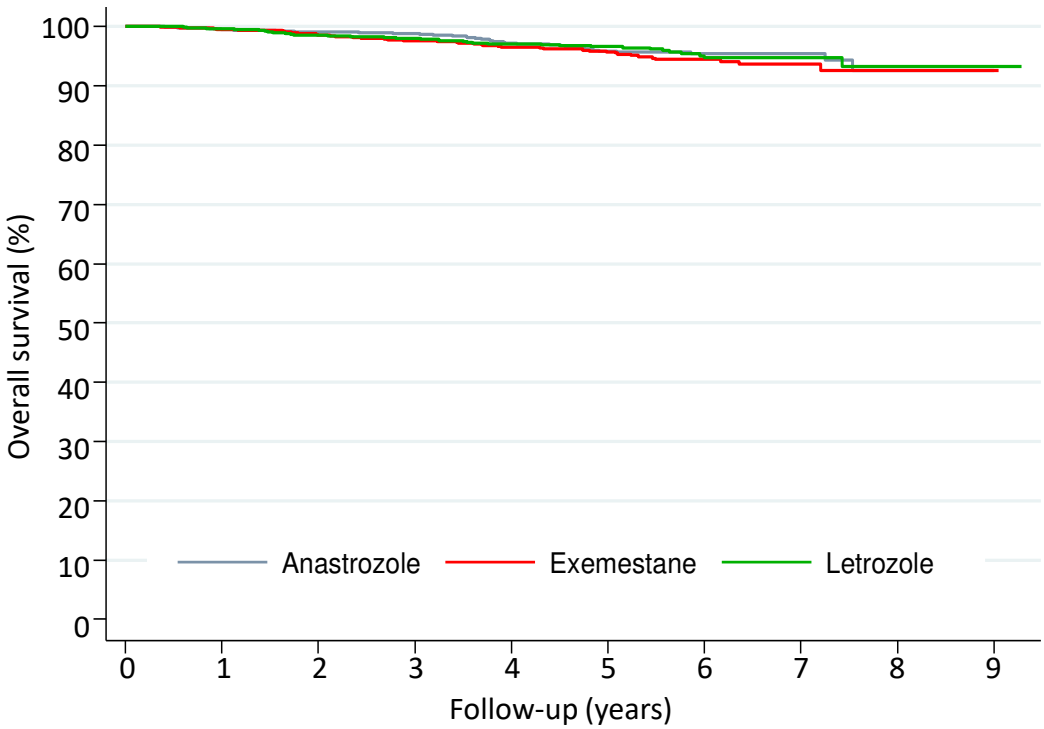
Figure 3a



Number at risk (number censored)

Anastrozole	1226 (0)	1149 (55)	1089 (83)	1013 (141)	840 (295)	546 (575)	289 (822)	127 (978)	18 (1084)	1 (1101)
Exemestane	1238 (0)	1140 (74)	1078 (99)	995 (157)	817 (312)	551 (561)	281 (818)	121 (971)	19 (1072)	2 (1088)
Letrozole	1233 (0)	1142 (67)	1077 (105)	985 (169)	819 (316)	553 (569)	270 (842)	118 (989)	25 (1079)	1 (1103)

Figure 3b



Number at risk (number censored)

Anastrozole	1226 (0)	1164 (57)	1127 (88)	1056 (157)	875 (322)	571 (616)	301 (884)	133 (1052)	21 (1162)	1 (1182)
Exemestane	1238 (0)	1155 (77)	1115 (107)	1033 (178)	851 (350)	581 (614)	300 (889)	133 (1054)	20 (1166)	2 (1184)
Letrozole	1233 (0)	1159 (70)	1102 (114)	1021 (189)	851 (350)	579 (619)	283 (908)	125 (1066)	26 (1164)	1 (1189)

Figure 3

Anastrozole versus exemestane versus letrozole, upfront or after 2 years of tamoxifen, as adjuvant treatment of breast cancer.

The FATA-GIM3 randomized phase III trial.

Web Appendix

Table A1. Baseline characteristics of patients by treatment arm

	Tam→Anastrozole N=611		Tam→Exemestane N=621		Tam→Letrozole N=618		Anastrozole N=615		Exemestane N=617		Letrozole N=615	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Age												
Median (IQR)	64	(59-70)	64	(59-70)	64	(57-70)	63	(57-70)	64	(58-70)	63	(47-70)
<60	184	(30·1)	175	(28·2)	197	(31·9)	207	(33·7)	190	(30·8)	199	(32·4)
60 - 69	264	(43·2)	264	(42·5)	240	(38·8)	240	(39·0)	259	(42·0)	243	(39·5)
70 +	163	(26·7)	182	(29·3)	181	(29·3)	168	(27·3)	168	(27·2)	173	(28·1)
Type of menopause		(0·0)		(0·0)		(0·0)		(0·0)		(0·0)		(0·0)
Over 60 or oophorectomy	429	(70·2)	452	(72·8)	428	(69·3)	413	(67·2)	433	(70·2)	425	(69·1)
<60 and >1yr amenorrhea	139	(22·7)	115	(18·5)	144	(23·3)	157	(25·5)	133	(21·6)	142	(23·1)
<60·and <1yr amenorrhea*	22	(3·6)	26	(4·2)	27	(4·4)	25	(4·1)	19	(3·1)	25	(4·1)
<60· unknown amenorrhea	21	(3·4)	28	(4·5)	19	(3·1)	20	(3·3)	32	(5·2)	23	(3·7)
Body Mass Index												
Median (IQR)	27·2	(24·3-31·0)	26·6	(23·7-30·1)	27·1	(24·2-31·2)	26·6	(23·9-30·5)	26·4	(24·0-30·5)	26·7	(23·7-30·1)
Underweight/Normal	15	(2·5)	19	(3·1)	20	(3·2)	16	(2·6)	18	(2·9)	16	(2·6)
Overweight	138	(22·6)	170	(27·4)	141	(22·8)	157	(25·5)	159	(25·8)	162	(26·3)
Obese	194	(31·8)	170	(27·4)	173	(28·0)	194	(31·5)	187	(30·3)	187	(30·4)
Unknown	148	(24·2)	126	(20·3)	158	(25·6)	137	(22·3)	143	(23·2)	130	(21·1)
Hormone receptors												
Both positive	546	(89·4)	551	(88·7)	549	(88·8)	548	(89·1)	548	(88·8)	546	(88·8)
Only one positive	65	(10·6)	70	(11·3)	69	(11·2)	67	(10·9)	69	(11·2)	69	(11·2)
HER-2 status												
Negative	550	(90·0)	557	(89·7)	556	(90·0)	555	(90·2)	557	(90·3)	557	(90·6)
Positive	53	(8·7)	59	(9·5)	56	(9·1)	54	(8·8)	55	(8·9)	53	(8·6)
Unknown	8	(1·3)	5	(0·8)	6	(1·0)	6	(1·0)	5	(0·8)	5	(0·8)

Table A1. (continued)

	Tam→Anastrozole N=611		Tam→Exemestane N=621		Tam→Letrozole N=618		Anastrozole N=615		Exemestane N=617		Letrozole N=615	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Pathologic nodal status												
pN0	392	(64·2)	402	(64·7)	397	(64·2)	396	(64·4)	397	(64·3)	394	(64·1)
pN1	156	(25·5)	154	(24·8)	155	(25·1)	155	(25·2)	154	(25·0)	154	(25·0)
pN2/pN3	63	(10·3)	65	(10·5)	66	(10·7)	64	(10·4)	66	(10·7)	67	(10·9)
Pathologic tumor category												
pT1	440	(72·0)	429	(69·1)	430	(69·6)	423	(68·8)	427	(69·2)	437	(71·1)
pT2	143	(23·4)	152	(24·5)	151	(24·4)	153	(24·9)	154	(25·0)	140	(22·8)
pT3/pT4	14	(2·3)	15	(2·4)	16	(2·6)	19	(3·1)	9	(1·5)	18	(2·9)
Unknown	14	(2·3)	25	(4·0)	21	(3·4)	20	(3·3)	27	(4·4)	20	(3·3)
Histologic grading												
Low	87	(14·2)	71	(11·4)	84	(13·6)	82	(13·3)	81	(13·1)	80	(13·0)
Intermediate	360	(58·9)	355	(57·2)	345	(55·8)	348	(56·6)	344	(55·8)	377	(61·3)
High	119	(19·5)	141	(22·7)	147	(23·8)	137	(22·3)	140	(22·7)	113	(18·4)
Unknown	45	(7·4)	54	(8·7)	42	(6·8)	48	(7·8)	52	(8·4)	45	(7·3)
Previous chemotherapy												
None	377	(61·7)	381	(61·4)	380	(61·5)	380	(61·8)	383	(62·1)	381	(62·0)
Adjuvant	219	(35·8)	224	(36·1)	222	(35·9)	219	(35·6)	220	(35·7)	219	(35·6)
Neoadjuvant	15	(2·5)	16	(2·6)	16	(2·6)	16	(2·6)	14	(2·3)	15	(2·4)
Trastuzumab												
No	551	(90·2)	551	(88·7)	556	(90·0)	556	(90·4)	547	(88·7)	559	(90·9)
Yes	45	(7·4)	42	(6·8)	43	(7·0)	43	(7·0)	45	(7·3)	38	(6·2)
Unknown	15	(2·5)	28	(4·5)	19	(3·1)	16	(2·6)	25	(4·1)	18	(2·9)
Radiotherapy												
No	194	(31·8)	174	(28·0)	174	(28·2)	200	(32·5)	158	(25·6)	177	(28·8)
Yes	402	(65·8)	419	(67·5)	425	(68·8)	399	(64·9)	434	(70·3)	420	(68·3)
Unknown	15	(2·5)	28	(4·5)	19	(3·1)	16	(2·6)	25	(4·1)	18	(2·9)

Table A2. Baseline metabolic profile of patients by treatment arm

	Tam→Anastrozole N=611	Tam→Exemestane N=621	Tam→Letrozole N=618	Anastrozole N=615	Exemestane N=617	Letrozole N=615
Cholesterol						
baseline value available (%)	321 (52·5)	304 (49·0)	312 (50·5)	307 (49·9)	322 (52·2)	304 (49·4)
median (IQR), mg/dL	216 (187-245)	214 (187-245)	212 (190-241)	217 (195-255)	221 (197-248)	213 (188-241)
Tryglicerides						
baseline value available (%)	282 (46·2)	268 (43·2)	286 (46·3)	274 (44·6)	306 (49·6)	273 (44·4)
median (IQR), mg/dL	120 (90-158)	111 (83-158)	120 (88-158)	114 (87-152)	117 (88-158)	115 (87-158)
Glycemia						
baseline value available (%)	131 (21·4)	130 (20·9)	126 (20·4)	121 (19·7)	129 (20·9)	129 (21·0)
median (IQR), mg/dL	98 (90-112)	98 (91-113)	99 (90-110)	97 (88-109)	99 (89-114)	96 (87-112)

Table A3. Baseline concomitant or previous comorbidity by treatment arm

	Tam→Anastrozole N=611		Tam→Exemestane N=621		Tam→Letrozole N=618		Anastrozole N=615		Exemestane N=617		Letrozole N=615	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Hypertension	249	(40·8)	241	(38·8)	266	(43·0)	239	(38·9)	237	(38·4)	252	(41·0)
Previous myocardial infarction	3	(0·5)	8	(1·3)	7	(1·1)	11	(1·8)	4	(0·6)	10	(1·6)
Ischemic heart disease	4	(0·7)	8	(1·3)	10	(1·6)	13	(2·1)	6	(1·0)	13	(2·1)
Arrhythmia	19	(3·1)	25	(4·0)	17	(2·8)	20	(3·3)	21	(3·4)	19	(3·1)
Cardiac failure	5	(0·8)	5	(0·8)	6	(1·0)	10	(1·6)	5	(0·8)	11	(1·8)
Coronary artery bypass grafting	2	(0·3)	4	(0·6)	4	(0·6)	8	(1·3)	2	(0·3)	6	(1·0)
Percutaneous transluminal coronary angioplasty	3	(0·5)	5	(0·8)	5	(0·8)	10	(1·6)	1	(0·2)	9	(1·5)
Valve replacement	4	(0·7)	7	(1·1)	6	(1·0)	9	(1·5)	3	(0·5)	8	(1·3)
Vascular stent	2	(0·3)	4	(0·6)	5	(0·8)	9	(1·5)	2	(0·3)	7	(1·1)
Brain vascular disease	5	(0·8)	8	(1·3)	5	(0·8)	10	(1·6)	4	(0·6)	8	(1·3)
Peripheral vascular disease	14	(2·3)	18	(2·9)	15	(2·4)	15	(2·4)	12	(1·9)	14	(2·3)
Previous cerebrovascular accident	4	(0·7)	6	(1·0)	6	(1·0)	10	(1·6)	5	(0·8)	6	(1·0)
Chronic obstructive pulmonary disease	5	(0·8)	8	(1·3)	7	(1·1)	13	(2·1)	3	(0·5)	11	(1·8)
Other pulmonary disease	9	(1·5)	15	(2·4)	14	(2·3)	18	(2·9)	7	(1·1)	16	(2·6)
Gastric ulcer	5	(0·8)	6	(1·0)	7	(1·1)	14	(2·3)	2	(0·3)	10	(1·6)
Gastritis	12	(2·0)	15	(2·4)	16	(2·6)	24	(3·9)	14	(2·3)	23	(3·7)
Cholelithiasis	19	(3·1)	25	(4·0)	19	(3·1)	25	(4·1)	13	(2·1)	18	(2·9)
Chronic hepatitis	11	(1·8)	11	(1·8)	9	(1·5)	14	(2·3)	8	(1·3)	12	(2·0)
Other gastro-intestinal disease	27	(4·4)	21	(3·4)	30	(4·9)	35	(5·7)	29	(4·7)	29	(4·7)
Chronic renal failure	5	(0·8)	5	(0·8)	5	(0·8)	7	(1·1)	2	(0·3)	7	(1·1)
Renal lithiasis	6	(1·0)	8	(1·3)	7	(1·1)	12	(2·0)	10	(1·6)	10	(1·6)
Other genito-urinary disease	15	(2·5)	27	(4·3)	15	(2·4)	23	(3·7)	17	(2·8)	20	(3·3)
Degenerative arthropathy	21	(3·4)	12	(1·9)	12	(1·9)	26	(4·2)	20	(3·2)	24	(3·9)
Other	145	(23·7)	156	(25·1)	171	(27·7)	161	(26·2)	169	(27·4)	161	(26·2)

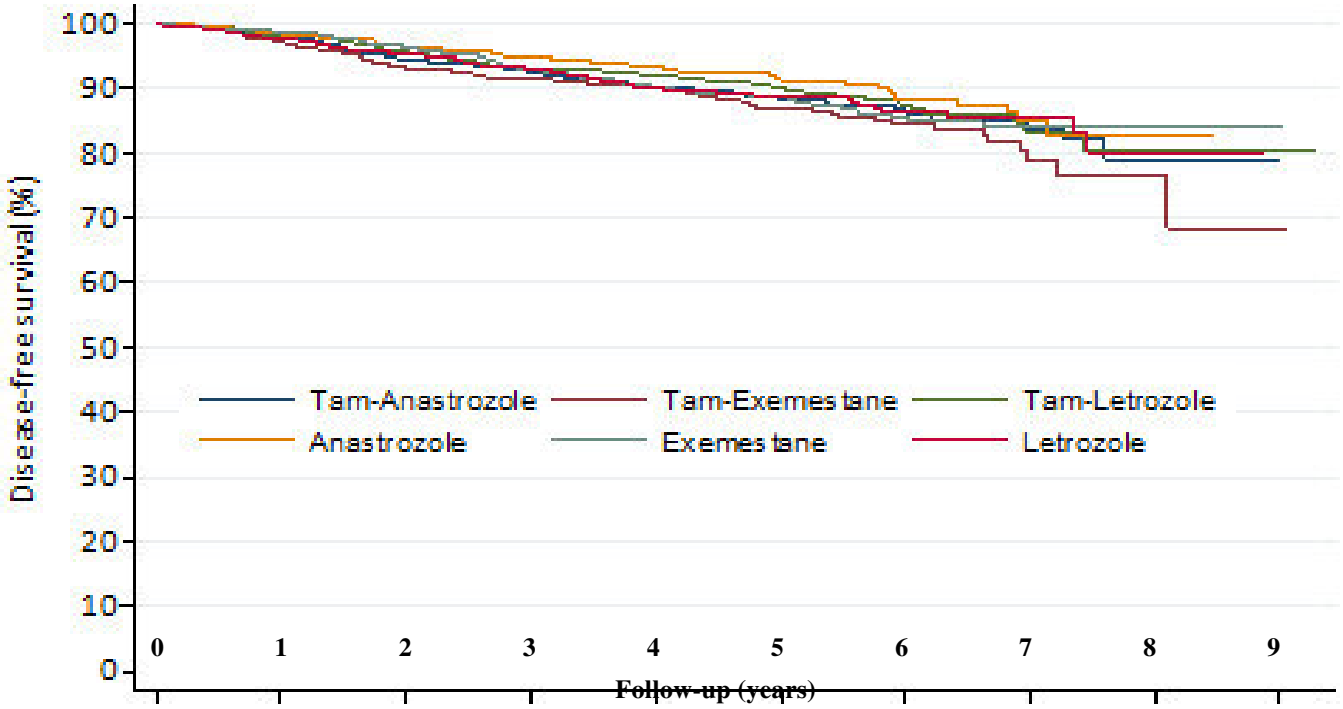
Table A4. Baseline information regarding bone health by treatment arm

	Tam→Anastrozole	Tam→Exemestane	Tam→Letrozole	Anastrozole	Exemestane	Letrozole
	N=611	N=621	N=618	N=615	N=617	N=615
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Bone status						
Normal	480 (78·6)	512 (82·4)	502 (81·2)	479 (77·9)	479 (77·6)	485 (78·9)
Osteopenia	74 (12·1)	60 (9·7)	78 (12·6)	90 (14·6)	78 (12·6)	79 (12·8)
Osteoporosis	57 (9·3)	49 (7·9)	38 (6·1)	46 (7·5)	60 (9·7)	51 (8·3)
Previous or ongoing drugs for bone health						
Calcium and/or Vitamin D	29 (4·7)	31 (5·0)	19 (3·1)	37 (6·0)	35 (5·7)	35 (5·7)
Biphosponates or Strontium	17 (2·8)	22 (3·5)	16 (2·6)	17 (2·8)	23 (3·7)	27 (4·4)

Table A5. Distribution of events by treatment arm

	Tam→Anastrozole N=611		Tam→Exemestane N=621		Tam→Letrozole N=618		Anastrozole N=615		Exemestane N=617		Letrozole N=615	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
DFS events	70	(11·5)	79	(12·7)	62	(10·0)	54	(8·8)	69	(11·2)	67	(10·9)
Type of DFS event												
Locoregional	7	(10·0)	16	(20·3)	7	(11·3)	5	(9·3)	14	(20·3)	7	(10·4)
Distant	36	(51·4)	34	(43·0)	29	(46·8)	27	(50·0)	23	(33·3)	34	(50·7)
Second breast cancer	7	(10·0)	3	(3·8)	3	(4·8)	5	(9·3)	8	(11·6)	3	(4·5)
Second non-breast cancer	12	(17·1)	18	(22·8)	14	(22·6)	14	(25·9)	11	(15·9)	11	(16·4)
Death without any cancer	8	(11·4)	8	(10·1)	9	(14·5)	3	(5·6)	13	(18·8)	12	(17·9)
Second non-breast cancers either as first or subsequent event	13	(2·1)	20	(3·2)	14	(2·3)	14	(2·3)	12	(1·9)	12	(2·0)
Type of second non-breast cancer												
Endometrial	3		3		4		1		1		1	
Endometrial	3		3		4		1		1		1	
Pulmonary	2		1		0		2		1		2	
Pancreatic	2		3		0		1		0		1	
Hematologic	0		2		1		1		2		0	
Renal	1		1		1		1		0		1	
Ovarian	1		1		2		0		0		1	
Hepatic	1		2		1		0		0		0	
Melanoma	0		2		0		0		0		1	
Urinary	0		0		1		0		2		0	
Other	1		2		0		2		2		2	
Deaths with or without cancer	28	(4·6)	32	(5·2)	20	(3·2)	15	(2·4)	20	(3·2)	23	(3·7)

Figure A1. Disease-free survival curves by treatment groups



Number at risk (number censored)

Tam-Anastrozole	611 (0)	564 (33)	535 (43)	498 (71)	412 (145)	268 (282)	146 (400)	72 (471)	12 (529)	1 (540)
Tam-Exemestane	621 (0)	565 (40)	530 (51)	487 (87)	397 (169)	268 (286)	135 (414)	57 (487)	12 (531)	1 (541)
Tam-Letrozole	618 (0)	581 (27)	546 (48)	497 (81)	416 (158)	277 (289)	126 (435)	55 (502)	10 (546)	1 (555)
Anastrozole	615 (0)	585 (22)	554 (40)	515 (70)	428 (150)	278 (293)	143 (422)	5 (507)	6 (555)	0 (561)
Exemestane	617 (0)	575 (34)	548 (48)	508 (70)	420 (143)	283 (275)	146 (404)	64 (484)	7 (541)	1 (547)
Latrozole	615 (0)	561 (40)	531 (57)	488 (88)	403 (158)	276 (280)	144 (407)	63 (487)	15 (533)	0 (548)

Figure A2. Forest plot of the effect of schedule on the HR of progression or death according to patient's and tumor's characteristics

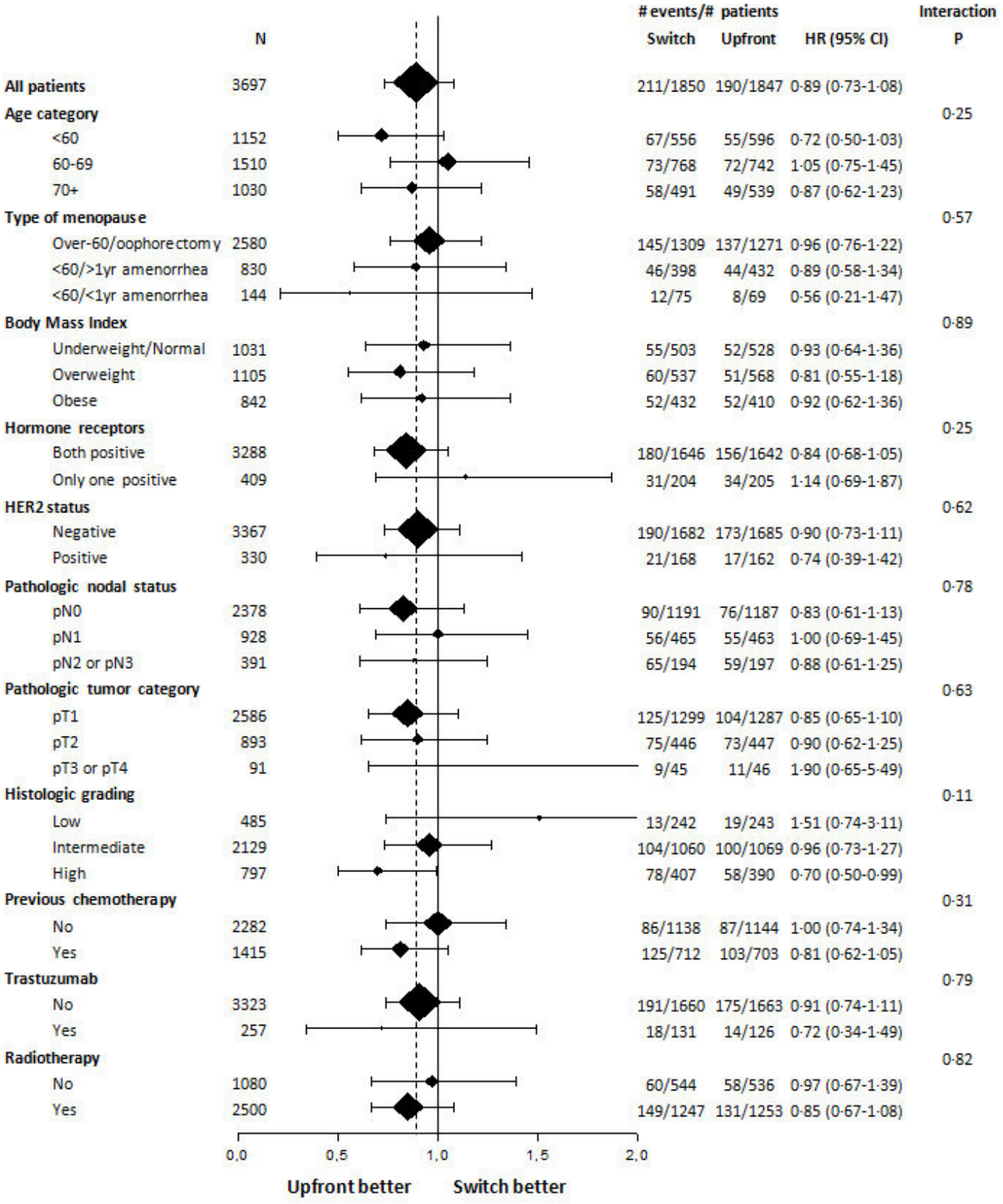
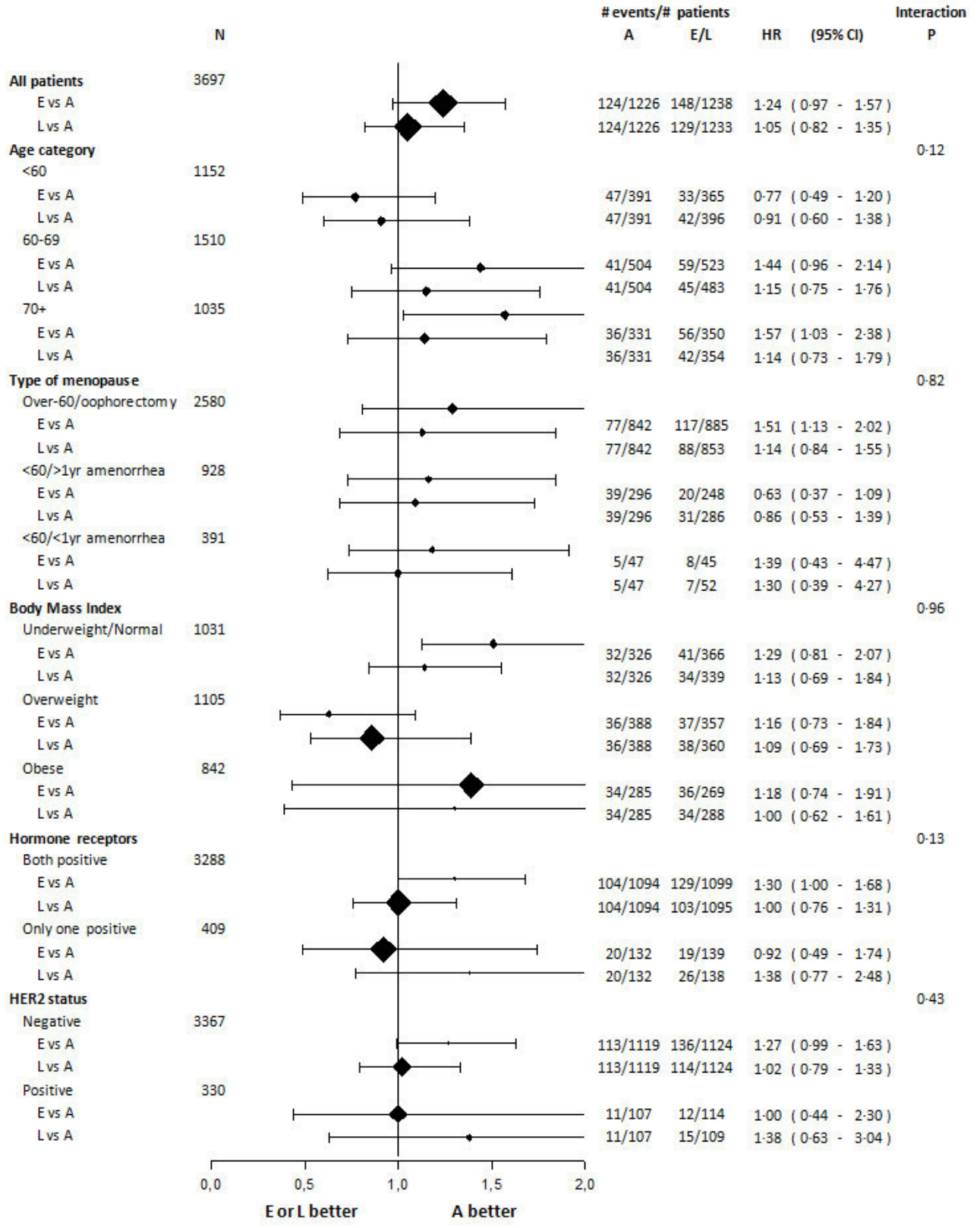
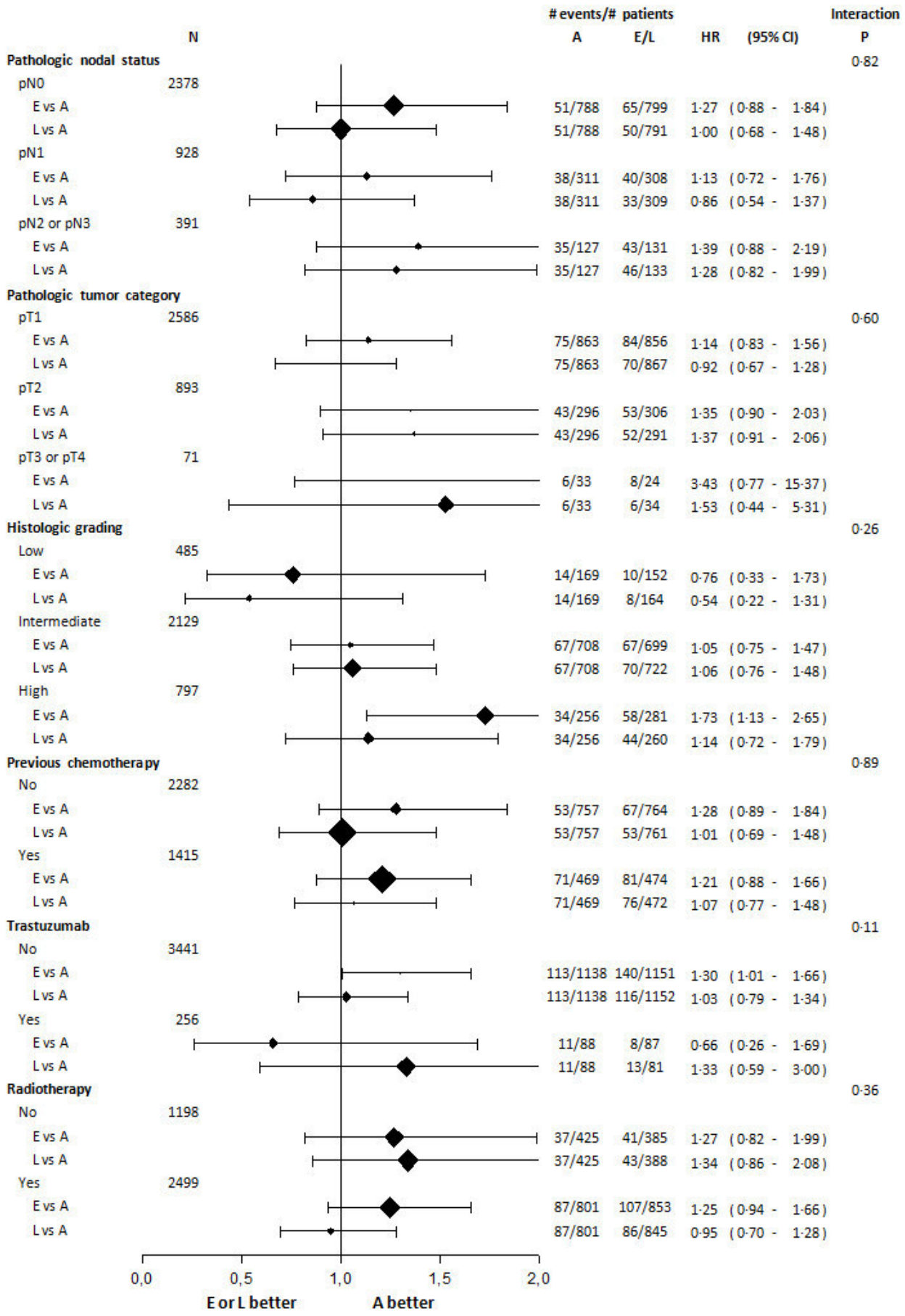


Figure A3. Forest plot of the effect of different aromatase inhibitors on the HR of progression or death according to patient's and tumor's characteristics.



A=anastrozole· E=Exemestane· L=Letrozole

Figure A3 (continued)



A=anastrozole· E=Exemestane· L=Letrozole

Table A6. Duration of treatment (months) with different drugs by treatment arm

	Tam→Anastrozole N=611	**Tam→Exemestane** N=621	**Tam→Letrozole** N=618	**Anastrozole** N=615	**Exemestane** N=617	**Letrozole** N=615
	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)	Median (IQR)
Time on Tamoxifen	24 (23-25)	24 (23-25)	24 (23-25)			
Time on Anastrozole	35 (30-36)			56 (53-60)		
Time on Exemestane		33 (27-36)			54 (53-60)	
Time on letrozole			32 (28-36)			54 (52-60)

Table A7. Causes of treatment interruption other than completed protocol by treatment arm

	Tam→Anastrozole	Tam→Exemestane	Tam→Letrozole	Anastrozole	Exemestane	Letrozole
	N=611	N=621	N=618	N=615	N=617	N=615
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Tamoxifen						
Death	3 (0·5)	2 (0·3)	4 (0·6)			
Relapse/second cancer	22 (3·6)	31 (5·0)	16 (2·6)			
Patient refusal	11 (1·8)	14 (2·3)	11 (1·8)			
Toxicity	74 (12·1)	61 (9·8)	69 (11·2)			
Other	22 (3·6)	13 (2·1)	16 (2·6)			
Aromatase inhibitors						
Death	4 (0·7)	5 (0·8)	2 (0·3)	4 (0·7)	8 (1·3)	5 (0·8)
Relapse/second cancer	23 (3·8)	13 (2·1)	17 (2·8)	29 (4·7)	44 (7·1)	36 (5·9)
Patient refusal	9 (1·5)	14 (2·3)	12 (1·9)	12 (2·0)	15 (2·4)	17 (2·8)
Toxicity	22 (3·6)	29 (4·7)	42 (6·8)	43 (7·0)	44 (7·1)	44 (7·2)
Other	23 (3·8)	24 (3·9)	21 (3·4)	19 (3·1)	23 (3·7)	21 (3·4)

Table A8. Details of toxicity reported in the Tamoxifen→Anastrozole treatment arm (N=578)

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
CARDIAC ARRHYTHMIA	24	(4·2)	9	(1·6)	2	(0·3)		
Supraventricular and nodal arrhythmia	13	(2·2)	5	(0·9)	1	(0·2)		
CARDIAC_GENERAL	101	(17·5)	37	(6·4)	6	(1·0)	1	(0·2)
Ischemia/infarction	1	(0·2)	1	(0·2)	1	(0·2)	1	(0·2)
Hypertension	95	(16·4)	34	(5·9)	3	(0·5)		
CONSTITUTIONAL	92	(15·9)	18	(3·1)	2	(0·3)		
Fatigue	57	(9·9)	13	(2·2)	2	(0·3)		
Sweating	6	(1·0)	1	(0·2)				
Weight gain	23	(4·0)	3	(0·5)				
DERMATOLOGY/SKIN	33	(5·7)	10	(1·7)	1	(0·2)		
Pruritus	11	(1·9)	5	(0·9)	1	(0·2)		
Dermatology other	9	(1·6)	3	(0·5)				
ENDOCRINE hot flushes	58	(10·0)	7	(1·2)				
GASTROINTESTINAL	56	(9·7)	11	(1·9)	1	(0·2)		
Nausea	15	(2·6)	3	(0·5)				
Constipation	10	(1·7)	1	(0·2)				
Gastritis	12	(2·1)	3	(0·5)				
Gastrointestinal other	14	(2·4)	5	(0·9)				
LYMPHATICS edema	25	(4·3)	4	(0·7)				
METABOLIC/LABORATORY	382	(66·1)	56	(9·7)	8	(1·4)	2	(0·3)
ALT/AST	13	(2·2)	6	(1·0)				
Cholesterol	336	(58·1)	16	(2·8)	1	(0·2)		
Glucose	208	(36·0)	29	(5·0)	9	(1·6)		
Triglyceride	191	(33·0)	7	(1·2)	1	(0·2)		
MUSCULOSKELETAL	176	(30·4)	72	(12·5)	39	(6·7)	1	(0·2)
Osteoporosis	61	(10·6)	17	(2·9)	29	(5·0)		
Arthritis	110	(19·0)	42	(7·3)	9	(1·6)		
Muscle weakness/pain	56	(9·7)	16	(2·8)	2	(0·3)		
Bone pain	92	(15·9)	29	(5·0)	3	(0·5)	1	(0·2)
NEUROLOGY	51	(8·8)	22	(3·8)	2	(0·3)		
Depression	26	(4·5)	9	(1·6)	1	(0·2)		
Anxiety	21	(3·6)	3	(0·5)				
CNS cerebrovascular ischemia			1	(0·2)	1	(0·2)		
Neurology other	12	(2·1)	6	(1·0)				
PAIN	13	(2·2)	3	(0·5)	1	(0·2)		
Headache	10	(1·7)	1	(0·2)				
Pain other	5	(0·9)	2	(0·3)	1	(0·2)		
PULMONARY	9	(1·6)	2	(0·3)				
RENAL/GENITOURINARY	4	(0·7)	7	(1·2)				
SEXUAL/REPRODUCTIVE FUNCTION	10	(1·7)	2	(0·3)				
Vaginal discharge	5	(0·9)	1	(0·2)				
Vaginal other	6	(1·0)	1	(0·2)				
VASCULAR	5	(0·9)	14	(2·4)	5	(0·9)		
Phlebitis			13	(2·2)				
Thrombosis/Embolism	2	(0·3)	5	(0·9)	4	(0·7)		
Endometrium	2	(0·3)	5	(0·9)	4	(0·7)		
Other event	14	(2·4)	2	(0·3)	4	(0·7)		

CTCAE categories are reported in capital letter and include the subcategories listed below. Categories and subcategories with less than 2% incidence in all the comparison arms and without statistically significant differences have not been reported in the table, with the exception of Ischemia/infarction e CNS cerebrovascular ischemia.

Table A9. Details of toxicity reported in the Tamoxifen→Exemestane treatment arm (N=589)

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
CARDIAC ARRHYTHMIA	14	(2·4)	3	(0·5)	2	(0·3)		
Supraventricular and nodal arrhythmia	5	(0·8)	3	(0·5)	1	(0·2)		
CARDIAC_GENERAL	70	(11·9)	37	(6·3)	5	(0·8)	1	(0·2)
Ischemia/infarction	1	(0·2)	1	(0·2)				
Hypertension	64	(10·9)	36	(6·1)	5	(0·8)		
CONSTITUTIONAL	73	(12·4)	18	(3·1)	2	(0·3)		
Fatigue	41	(7·0)	10	(1·7)	1	(0·2)		
Sweating	9	(1·5)	2	(0·3)				
Weight gain	25	(4·2)	4	(0·7)	1	(0·2)		
DERMATOLOGY/SKIN	34	(5·8)	10	(1·7)	1	(0·2)		
Pruritus	13	(2·2)	5	(0·8)				
Dermatology other	12	(2·0)	4	(0·7)				
ENDOCRINE hot flushes	48	(8·1)	18	(3·1)				
GASTROINTESTINAL	70	(11·9)	11	(1·9)	4	(0·7)		
Nausea	17	(2·9)	4	(0·7)				
Constipation	25	(4·2)	1	(0·2)	1	(0·2)		
Gastritis	11	(1·9)	6	(1·0)	2	(0·3)		
Gastrointestinal other	18	(3·1)	3	(0·5)	1	(0·2)		
LYMPHATICS edema	27	(4·6)	3	(0·5)	1	(0·2)		
METABOLIC/LABORATORY	359	(61·0)	49	(8·3)	6	(1·0)	2	(0·3)
ALT/AST	9	(1·5)	5	(0·8)	1	(0·2)		
Cholesterol	318	(54·0)	9	(1·5)	1	(0·2)	1	(0·2)
Glucose	180	(30·6)	26	(4·4)	4	(0·7)		
Triglyceride	155	(26·3)	11	(1·9)	1	(0·2)		
MUSCULOSKELETAL	187	(31·7)	65	(11·0)	46	(7·8)	1	(0·2)
Osteoporosis	67	(11·4)	20	(3·4)	33	(5·6)		
Arthritis	104	(17·7)	32	(5·4)	9	(1·5)	1	(0·2)
Muscle weakness/pain	59	(10·0)	17	(2·9)				
Bone pain	94	(16·0)	31	(5·3)	5	(0·8)		
NEUROLOGY	43	(7·3)	16	(2·7)	6	(1·0)	1	(0·2)
Depression	18	(3·1)	10	(1·7)	2	(0·3)		
Anxiety	16	(2·7)	5	(0·8)	2	(0·3)		
CNS cerebrovascular ischemia					3	(0·5)	1	(0·2)
Neurology other	14	(2·4)	1	(0·2)	1	(0·2)		
PAIN	25	(4·2)	2	(0·3)	1	(0·2)		
Headache	12	(2·0)	2	(0·3)	1	(0·2)		
Pain other	14	(2·4)						
PULMONARY	6	(1·0)			1	(0·2)		
RENAL/GENITOURINARY	2	(0·3)	3	(0·5)				
SEXUAL/REPRODUCTIVE FUNCTION	16	(2·7)	1	(0·2)				
Vaginal discharge	9	(1·5)						
Vaginal other	7	(1·2)	1	(0·2)				
VASCULAR	5	(0·8)	13	(2·2)	4	(0·7)	1	(0·2)
Phlebitis			12	(2·0)				
Thrombosis/Embolism	3	(0·5)	2	(0·3)	4	(0·7)	1	(0·2)
Endometrium	16	(2·7)	7	(1·2)	1	(0·2)		
Other event	16	(2·7)	8	(1·4)	5	(0·8)		

CTCAE categories are reported in capital letter and include the subcategories listed below. Categories and subcategories with less than 2% incidence in all the comparison arms and without statistically significant differences have not been reported in the table, with the exception of Ischemia/infarction e CNS cerebrovascular ischemia.

Table A10. Details of toxicity reported in the Tamoxifen→Letrozole treatment arm (N=594)

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
CARDIAC ARRHYTHMIA	15	(2·5)	6	(1·0)	3	(0·5)		
Supraventricular and nodal arrhythmia	5	(0·8)	2	(0·3)	1	(0·2)		
CARDIAC_GENERAL	85	(14·3)	38	(6·4)	5	(0·8)	1	(0·2)
Ischemia/infarction	1	(0·2)	1	(0·2)				
Hypertension	78	(13·1)	35	(5·9)	3	(0·5)		
CONSTITUTIONAL	77	(13·0)	16	(2·7)				
Fatigue	47	(7·9)	10	(1·7)				
Sweating	8	(1·3)						
Weight gain	31	(5·2)	3	(0·5)				
DERMATOLOGY/SKIN	33	(5·6)	8	(1·3)	2	(0·3)		
Pruritus	14	(2·4)	3	(0·5)	1	(0·2)		
Dermatology other	8	(1·3)	2	(0·3)	1	(0·2)		
ENDOCRINE hot flushes	43	(7·2)	19	(3·2)				
GASTROINTESTINAL	32	(5·4)	10	(1·7)	1	(0·2)		
Nausea	5	(0·8)	2	(0·3)				
Constipation	12	(2·0)	2	(0·3)				
Gastritis	6	(1·0)	2	(0·3)				
Gastrointestinal other	4	(0·7)	2	(0·3)				
LYMPHATICS edema	21	(3·5)	7	(1·2)				
METABOLIC/LABORATORY	368	(62·0)	73	(12·3)	9	(1·5)	4	(0·7)
ALT/AST	15	(2·5)	5	(0·8)	2	(0·3)		
Cholesterol	329	(55·4)	27	(4·5)			2	(0·3)
Glucose	208	(35·0)	36	(6·1)	4	(0·7)	1	(0·2)
Triglyceride	167	(28·1)	12	(2·0)	3	(0·5)	1	(0·2)
MUSCULOSKELETAL	159	(26·8)	86	(14·5)	43	(7·2)		
Osteoporosis	66	(11·1)	17	(2·9)	33	(5·6)		
Arthritis	91	(15·3)	50	(8·4)	8	(1·3)		
Muscle weakness/pain	60	(10·1)	17	(2·9)	3	(0·5)		
Bone pain	90	(15·2)	37	(6·2)	5	(0·8)		
NEUROLOGY	50	(8·4)	23	(3·9)	3	(0·5)	4	(0·7)
Depression	22	(3·7)	16	(2·7)	1	(0·2)		
Anxiety	19	(3·2)	4	(0·7)				
CNS cerebrovascular ischemia							4	(0·7)
Neurology other	10	(1·7)	4	(0·7)	2	(0·3)		
PAIN	10	(1·7)	6	(1·0)				
Headache	5	(0·8)	3	(0·5)				
Pain other	5	(0·8)	3	(0·5)				
PULMONARY	8	(1·3)	3	(0·5)	2	(0·3)		
RENAL/GENITOURINARY	4	(0·7)	2	(0·3)				
SEXUAL/REPRODUCTIVE FUNCTION	17	(2·9)	6	(1·0)				
Vaginal discharge	8	(1·3)	1	(0·2)				
Vaginal other	9	(1·5)	5	(0·8)				
VASCULAR	9	(1·5)	6	(1·0)	5	(0·8)	1	(0·2)
Phlebitis			6	(1·0)				
Thrombosis/Embolism	2	(0·3)	6	(1·0)	1	(0·2)	1	(0·2)
Endometrium	13	(2·2)	9	(1·5)	3	(0·5)		
Other event	16	(2·7)	11	(1·9)	1	(0·2)		

CTCAE categories are reported in capital letter and include the subcategories listed below. Categories and subcategories with less than 2% incidence in all the comparison arms and without statistically significant differences have not been reported in the table, with the exception of Ischemia/infarction e CNS cerebrovascular ischemia.

Table A11. Details of toxicity reported in the Anastrozole treatment arm (N=597)

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
CARDIAC ARRHYTHMIA	13	(2·2)	10	(1·7)				
Supraventricular and nodal arrhythmia	6	(1·0)	5	(0·8)				
CARDIAC_GENERAL	74	(12·4)	34	(5·7)	8	(1·3)	2	(0·3)
Ischemia/infarction			2	(0·3)	1	(0·2)	2	(0·3)
Hypertension	65	(10·9)	32	(5·4)	7	(1·2)		
CONSTITUTIONAL	69	(11·6)	21	(3·5)	2	(0·3)		
Fatigue	46	(7·7)	12	(2·0)	1	(0·2)		
Sweating	4	(0·7)	2	(0·3)				
Weight gain	18	(3·0)	3	(0·5)	1	(0·2)		
DERMATOLOGY/SKIN	13	(2·2)	9	(1·5)				
Pruritus	5	(0·8)	1	(0·2)				
Dermatology other	4	(0·7)	4	(0·7)				
ENDOCRINE hot flushes	34	(5·7)	11	(1·8)				
GASTROINTESTINAL	38	(6·4)	8	(1·3)	2	(0·3)		
Nausea	9	(1·5)	2	(0·3)				
Constipation	12	(2·0)	2	(0·3)				
Gastritis	12	(2·0)	2	(0·3)				
Gastrointestinal other	9	(1·5)			2	(0·3)		
LYMPHATICS edema	22	(3·7)	6	(1·0)				
METABOLIC/LABORATORY	401	(67·2)	65	(10·9)	8	(1·3)	1	(0·2)
ALT/AST	10	(1·7)	4	(0·7)				
Cholesterol	363	(60·8)	34	(5·7)	1	(0·2)	1	(0·2)
Glucose	215	(36·0)	26	(4·4)	7	(1·2)		
Triglyceride	137	(22·9)	7	(1·2)				
MUSCULOSKELETAL	215	(36·0)	95	(15·9)	42	(7·0)		
Osteoporosis	92	(15·4)	31	(5·2)	23	(3·9)		
Arthritis	130	(21·8)	48	(8·0)	10	(1·7)		
Muscle weakness/pain	60	(10·1)	18	(3·0)	4	(0·7)		
Bone pain	103	(17·3)	47	(7·9)	9	(1·5)		
NEUROLOGY	50	(8·4)	15	(2·5)	6	(1·0)		
Depression	14	(2·3)	9	(1·5)	2	(0·3)		
Anxiety	17	(2·8)	2	(0·3)	1	(0·2)		
CNS cerebrovascular ischemia			1	(0·2)	1	(0·2)		
Neurology other	19	(3·2)	3	(0·5)	3	(0·5)		
PAIN	16	(2·7)	5	(0·8)				
Headache	11	(1·8)	4	(0·7)				
Pain other	7	(1·2)	1	(0·2)				
PULMONARY	9	(1·5)	3	(0·5)	2	(0·3)		
RENAL/GENITOURINARY	4	(0·7)	5	(0·8)	3	(0·5)		
SEXUAL/REPRODUCTIVE FUNCTION	4	(0·7)						
Vaginal discharge	2	(0·3)						
Vaginal other	2	(0·3)						
VASCULAR	7	(1·2)	4	(0·7)	1	(0·2)		
Phlebitis			5	(0·8)				
Thrombosis/Embolism	2	(0·3)	2	(0·3)	1	(0·2)		
Endometrium	1	(0·2)	2	(0·3)	1	(0·2)		
Other event	17	(2·8)	8	(1·3)	1	(0·2)		

CTCAE categories are reported in capital letter and include the subcategories listed below. Categories and subcategories with less than 2% incidence in all the comparison arms and without statistically significant differences have not been reported in the table, with the exception of Ischemia/infarction e CNS cerebrovascular ischemia.

Table A12. Details of toxicity reported in the Exemestane treatment arm (N=588)

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
CARDIAC ARRHYTHMIA	20	(3·4)	8	(1·4)	3	(0·5)		
Supraventricular and nodal arrhythmia	6	(1·0)	1	(0·2)	2	(0·3)		
CARDIAC_GENERAL	74	(12·6)	46	(7·8)	7	(1·2)	1	(0·2)
Ischemia/infarction	1	(0·2)	2	(0·3)	2	(0·3)	1	(0·2)
Hypertension	72	(12·2)	43	(7·3)	3	(0·5)		
CONSTITUTIONAL	73	(12·4)	23	(3·9)	3	(0·5)		
Fatigue	41	(7·0)	14	(2·4)	2	(0·3)		
Sweating	11	(1·9)	2	(0·3)				
Weight gain	24	(4·1)	3	(0·5)	1	(0·2)		
DERMATOLOGY/SKIN	26	(4·4)	9	(1·5)	2	(0·3)		
Pruritus	10	(1·7)	2	(0·3)	1	(0·2)		
Dermatology other	10	(1·7)	6	(1·0)	1	(0·2)		
ENDOCRINE hot flushes	50	(8·5)	10	(1·7)				
GASTROINTESTINAL	41	(7·0)	14	(2·4)	4	(0·7)		
Nausea	13	(2·2)	2	(0·3)				
Constipation	13	(2·2)	1	(0·2)				
Gastritis	9	(1·5)	3	(0·5)	1	(0·2)		
Gastrointestinal other	13	(2·2)	3	(0·5)	1	(0·2)		
LYMPHATICS edema	15	(2·6)	2	(0·3)	1	(0·2)		
METABOLIC/LABORATORY	392	(66·7)	52	(8·8)	7	(1·2)	1	(0·2)
ALT/AST	11	(1·9)	2	(0·3)	3	(0·5)		
Cholesterol	351	(59·7)	18	(3·1)				
Glucose	191	(32·5)	32	(5·4)	3	(0·5)	1	(0·2)
Triglyceride	142	(24·1)	5	(0·9)	1	(0·2)		
MUSCULOSKELETAL	196	(33·3)	115	(19·6)	36	(6·1)	1	(0·2)
Osteoporosis	72	(12·2)	37	(6·3)	20	(3·4)		
Arthritis	134	(22·8)	61	(10·4)	15	(2·6)	1	(0·2)
Muscle weakness/pain	82	(13·9)	27	(4·6)	1	(0·2)		
Bone pain	109	(18·5)	44	(7·5)	3	(0·5)		
NEUROLOGY	53	(9·0)	16	(2·7)	2	(0·3)	2	(0·3)
Depression	25	(4·3)	7	(1·2)	1	(0·2)		
Anxiety	15	(2·6)	4	(0·7)				
CNS cerebrovascular ischemia			1	(0·2)			2	(0·3)
Neurology other	18	(3·1)	4	(0·7)	1	(0·2)		
PAIN	10	(1·7)	3	(0·5)				
Headache	2	(0·3)	3	(0·5)				
Pain other	9	(1·5)						
PULMONARY	8	(1·4)	3	(0·5)	2	(0·3)		
RENAL/GENITOURINARY	4	(0·7)	1	(0·2)				
SEXUAL/REPRODUCTIVE FUNCTION	4	(0·7)						
Vaginal discharge	3	(0·5)						
Vaginal other	1	(0·2)						
VASCULAR	6	(1·0)	5	(0·9)	1	(0·2)		
Phlebitis			7	(1·2)				
Thrombosis/Embolism	4	(0·7)	1	(0·2)				
Endometrium	4	(0·7)						
Other event	17	(2·9)	6	(1·0)	1	(0·2)		

CTCAE categories are reported in capital letter and include the subcategories listed below. Categories and subcategories with less than 2% incidence in all the comparison arms and without statistically significant differences have not been reported in the table, with the exception of Ischemia/infarction e CNS cerebrovascular ischemia.

Table A13. Details of toxicity reported in the Letrozole treatment arm (N=581)

	Grade 1		Grade 2		Grade 3		Grade 4	
	n	*(%)*	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
CARDIAC ARRHYTHMIA	19	(3·3)	7	(1·2)				
Supraventricular and nodal arrhythmia	8	(1·4)	1	(0·2)				
CARDIAC_GENERAL	74	(12·7)	40	(6·9)	5	(0·9)		
Ischemia/infarction	1	(0·2)	2	(0·3)	3	(0·5)		
Hypertension	68	(11·7)	37	(6·4)	2	(0·3)		
CONSTITUTIONAL	77	(13·3)	20	(3·4)	3	(0·5)		
Fatigue	44	(7·6)	9	(1·5)	2	(0·3)		
Sweating	5	(0·9)	1	(0·2)				
Weight gain	27	(4·6)	1	(0·2)				
DERMATOLOGY/SKIN	25	(4·3)	8	(1·4)	3	(0·5)		
Pruritus	13	(2·2)	2	(0·3)	3	(0·5)		
Dermatology other	6	(1·0)	3	(0·5)	1	(0·2)		
ENDOCRINE hot flushes	36	(6·2)	4	(0·7)				
GASTROINTESTINAL	38	(6·5)	6	(1·0)	2	(0·3)		
Nausea	12	(2·1)						
Constipation	9	(1·5)						
Gastritis	9	(1·5)	2	(0·3)	1	(0·2)		
Gastrointestinal other	8	(1·4)	3	(0·5)	1	(0·2)		
LYMPHATICS edema	19	(3·3)	2	(0·3)	1	(0·2)		
METABOLIC/LABORATORY	385	(66·3)	62	(10·7)	8	(1·4)	4	(0·7)
ALT/AST	13	(2·2)	5	(0·9)				
Cholesterol	356	(61·3)	32	(5·5)	3	(0·5)	4	(0·7)
Glucose	179	(30·8)	23	(4·0)	4	(0·7)		
Triglyceride	157	(27·0)	10	(1·7)	1	(0·2)		
MUSCULOSKELETAL	203	(34·9)	100	(17·2)	47	(8·1)	2	(0·3)
Osteoporosis	81	(13·9)	35	(6·0)	31	(5·3)		
Arthritis	138	(23·8)	46	(7·9)	11	(1·9)	1	(0·2)
Muscle weakness/pain	78	(13·4)	21	(3·6)	3	(0·5)		
Bone pain	116	(20·0)	39	(6·7)	11	(1·9)	2	(0·3)
NEUROLOGY	54	(9·3)	23	(4·0)	5	(0·9)	1	(0·2)
Depression	17	(2·9)	9	(1·5)	2	(0·3)	1	(0·2)
Anxiety	15	(2·6)	2	(0·3)	1	(0·2)		
CNS cerebrovascular ischemia								
Neurology other	19	(3·3)	10	(1·7)	2	(0·3)		
PAIN	25	(4·3)	3	(0·5)				
Headache	13	(2·2)	2	(0·3)				
Pain other	15	(2·6)	1	(0·2)				
PULMONARY	6	(1·0)	2	(0·3)	1	(0·2)		
RENAL/GENITOURINARY	7	(1·2)	2	(0·3)	1	(0·2)		
SEXUAL/REPRODUCTIVE FUNCTION	6	(1·0)	2	(0·3)				
Vaginal discharge	3	(0·5)	2	(0·3)				
Vaginal other	3	(0·5)						
VASCULAR	7	(1·2)	7	(1·2)	3	(0·5)		
Phlebitis			6	(1·0)				
Thrombosis/Embolism	1	(0·2)	4	(0·7)	2	(0·3)		
Endometrium	3	(0·5)	1	(0·2)				
Other event	11	(1·9)	7	(1·2)	3	(0·5)	1	(0·2)

CTCAE categories are reported in capital letter and include the subcategories listed below. Categories and subcategories with less than 2% incidence in all the comparison arms and without statistically significant differences have not been reported in the table, with the exception of Ischemia/infarction e CNS cerebrovascular ischemia.

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- Centro di Riferimento Oncologico della Basilicata CROB, Unità Operativa di Oncologia Medica, Rionero In Vulture (Michele Aieta, Mariarosa Coccaro, Carmen Romano)
- Università della Campania Luigi Vanvitelli, UOC Oncoematologia, Napoli (Fortunato Ciardiello, Michele Orditura, Anna Diana)
- Ospedale Civile – ASL1, Oncologia Medica, Città di Castello (Luigi Castori, Stefano Bravi, Michele Montedoro)
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- Ospedale Bufalini, Oncologia Medica, Cesena (Marina Faedi)
- Azienda USL - Ospedale S.Anna, Day Hospital Oncologico, Castelnuovo Nei Monti (Roberto Vignoli, Alda Zanni)
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- Ospedale Civile, Ginecologia, Bressanone (Verena Thalmann, Sonia Prader)
- Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (I.R.S.T.), Oncologia, Meldola (Dino Amadori)
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- Ospedale S.Croce Asur 3, Oncologia Medica, Fano (Silvia Pelliccioni, Claudia Cappelletti)
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- Azienda Ospedale San Salvatore, Oncologia Medica, Pesaro (Virginia Casadei)
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Institution enrolling patients	PI	# patients
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Arcispedale Santa Maria Nuova, Oncologia Medica Senologica, Reggio Emilia	Giancarlo Bisagni (previous PI: Corrado Boni)	274
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Ospedale Cardarelli, UO Oncologia Medica, Napoli	Ferdinando Riccardi	158
Ospedale Policlinico San Martino – IRCCS per l'oncologia, Dipartimento di Oncologia Medica, UO Sviluppo Terapie Innovative, Genova	Lucia Del Mastro	128
Azienda Ospedaliera Universitaria, Oncologia Medica, Sassari	Antonio Pazzola	119
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Azienda Ospedaliera S.Anna, UO Oncologia, Ferrara	Antonio Frassoldati	89
Ospedale Unico Versilia, UO Oncologia Medica, Lido di Camaiore	Domenico Amoroso	71
Presidio Ospedaliero "F. Renzetti" USL Lanciano-Vasto-Chieti, UO Oncologia Medica, Lanciano	Lucio Laudadio	69
Presidio Ospedaliero `Belcolle`, UOC Oncologia Medica, Viterbo	Luca Moscetti	68
IRCCS- Istituti Clinici Scientifici Maugeri, UO Oncologia Medica, Pavia	Antonio Bernardo	61
IRCC - Istituto per la Ricerca e la Cura del Cancro, Divisione Oncologia Medica, Candiolo	Filippo Montemurro	60
Azienda Ospedaliera, SC Oncologia Medica, Saronno	Claudio Verusio	59
Polo Oncologico, Oncologia. Lecce	Vito Lorusso	58
Ospedale Civile A. Cardarelli, UOC Oncologia Medica, Campobasso	Francesco Carrozza	55
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Azienda Ospedaliera Fatebenefratelli ed Oftalmico, Divisione di Oncologia Medica E Chemioterapia, Milano	Gabriella Farina	51
Ospedale Civile, Oncologia Medica, Faenza	Angelo Gambi	46
Ospedale Clinicizzato `S.Annunziata` - Università Degli Studi `G. D'annunzio`, Oncologia Medica, Chieti	Clara Natoli	45
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Ospedale Civile – ASL1, Oncologia Medica, Città di Castello	Luigi Castori	30
Ospedale Fatebenefratelli Benevento, Oncologia Medica, Benevento	Antonio Febbraro	26
Ospedale Bufalini, Oncologia Medica, Cesena	Marina Faedi	26

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Università Campus Biomedico, Oncologia Medica, Roma	Giuseppe Tonini	5
Azienda Unità Sanitaria Locale di Piacenza, Day Hospital Onco-Ematologico, Piacenza	Luigi Cavanna	5
Azienda Ospedaliera Santa Maria Degli Angeli, Oncologia Medica, Pordenone	Silvana Saracchini	4
Università Politecnica Delle Marche, Clinica di Oncologia Medica, Ancona	Rossana Berardi	3
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EUDRACT number: 2006-004018-42

AIFA code: FARM5K3MEE

Protocol title:

A phase III study comparing anastrozole, letrozole and exemestane, upfront (for 5 years) or sequentially (for 3 years after 2 years of tamoxifen), as adjuvant treatment of postmenopausal patients with endocrine-responsive breast cancer.

Nickname:

GIM3-FATA – First Adjuvant Trial on All aromatase inhibitors in early breast cancer.

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Chair of the Statistical Analysis Committee:	Ciro Gallo, MD (Napoli, Italy)
Chair of the Data Coordinating Committee:	Francesco Perrone, MD, PhD (Napoli, Italy)
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Responsible of pharmacovigilance:	Gianfranco Di Renzo, MD (Napoli, Italy)
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Sponsor non-profit:	Dipartimento di endocrinologia ed Oncologia Molecolare e Clinica- Università Federico II, Napoli, Italy
Supported by:	AIFA (Italian Drug Agency) grant no. FARM5K3MEE
Coordinating Ethical Committee:	IEC of the University Federico II, Napoli, Italy

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Protocol Synopsis

Title of the Study	FATA – **F**IRST **A**DJUVANT **T**RIAL ON **A**LL AROMATASE INHIBITORS IN EARLY BREAST CANCER. A PHASE 3 STUDY COMPARING ANASTROZOLE, LETROZOLE AND EXEMESTANE, UPFRONT (FOR 5 YEARS) OR SEQUENTIALLY (FOR 3 YEARS AFTER 2 YEARS OF TAMOXIFEN), AS ADJUVANT TREATMENT OF POSTMENOPAUSAL PATIENTS WITH ENDOCRINE-RESPONSIVE BREAST CANCER.
Study Chairmen	Sabino de Placido, MD, (Napoli, Italy)
Study timetable	Planned start date: October 2006 Planned accrual time: 4 years
Study design	Multicenter, open label, six arms factorial phase III randomized study comparing anastrozole, letrozole and exemestane used upfront (for 5 years) arms A, B, C or sequentially (for 3 years after 2 years of tamoxifen) arms D, E, F, as adjuvant treatment of postmenopausal patients with endocrine-responsive breast cancer.
Objectives	Primary objectives: to compare the disease free survival (DFS) in patients treated with: • sequential (tamoxifen 2 yrs →AIs 3yrs) vs upfront (AIs 5yrs) strategy of treatment • Anastrozole vs exemestane vs letrozole Secondary objectives: To compare Distant-metastasis-free survival, cumulative incidence of contralateral breast cancer as first event, breast cancer-free survival, overall survival, cumulative incidence and type of second non-breast invasive cancer, toxicity.
Methodology	Open label, randomized, multicenter phase III study. Randomization process will be performed by a WEB based procedure
Number of subjects	Up to 3600 pts will be enrolled to detect an absolute 2% difference of DFS-DCIS at 5 years (corresponding to a HR of 0.7914), with 2-sided significance level of 0.05, power of 0.80 and three interim analysis.
Patients selection	Inclusion criteria - Women with histological diagnosis of invasive breast cancer completely removed by surgery, any T, any N. - Postmenopausal status defined by at least one of the following conditions: 1. Aged ≥ 60 2. Aged 45-59 and satisfying one or more of the following criteria • amenorrhea for ≥12 months and intact uterus; • amenorrhea for <12 months and FSH within the postmenopausal range, including: ▪ pts with hysterectomy ▪ pts who have received HRT ▪ pts with chemotherapy-induced amenorrhea 3. bilateral oophorectomy at any age >18 years. - Primary tumor positive for ER or PgR (≥10% tumor cells positive by immunoistochemistry or ≥ 10 fmol/mg cytosol protein by ligand binding assay). - Adjuvant/ neoadjuvant chemotherapy, if given, must be completed before enrolment. - Patients with HER-2 positive tumors are eligible provided that they receive trastuzumab according to registered schedule. - Signed informed consent. Exclusion criteria - HRT concurrent or assumed during the month before randomization

	- Recurrent or metastatic disease - HER-2 positive tumors if treatment with trastuzumab is not feasible - Concurrent illness that contraindicate adjuvant endocrine treatment - Patients who have received TAM as part of any breast cancer prevention trial - Previous history of invasive breast cancer or other invasive malignancy within the previous 10 years, other than squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied - Concomitant severe disease which would place the patient at unusual risk - Concurrent treatment with other experimental drugs - Patients treated with systemic investigational drugs within the past 30 days
Test drug: dose and mode of administration	Anastrozole (1 mg tablets) or exemestane (25 mg tablets) or letrozole (2.5 mg tablets), once daily, for 5 years Tamoxifen (20 mg tablets) once daily for 2 years followed by anastrozole (1 mg tablets) or exemestane (25 mg tablets) or letrozole (2.5 mg tablets), once daily, for 3 years
Criteria of evaluation	Disease-free survival (DFS) defined as the time elapsed from randomization to the first among the following events: • local or regional relapse • distant metastasis • contralateral breast cancer • other invasive cancer different than breast • death. Survival defined as time elapsing between the date of randomization and the date of death for any cause Safety: Clinical and laboratory toxicities will be graded according to NCI criteria CTCAE (Common Terminology Criteria for Adverse Events of National Cancer Institute v.3.0). The adverse events witch are not reported in NCI criteria will be graded as: mild (1), moderate (2), severe (3), and life threatening (4)

Background and rationale

Breast cancer is the most common form of cancer among women in North America, Europe and Latin America. Incidence rates generally are highest in North America and northern European countries. Hormonal therapy is a mainstay of treatment of advanced breast cancer in postmenopausal women. Tamoxifen, a selective estrogen receptor modulator, has been for many years the agent of choice because it is well tolerated and produces significant responses in many patients. It is generally accepted that patients with early breast cancer should be treated with adjuvant systemic therapy. In postmenopausal patients with hormone receptor positive tumors, adjuvant tamoxifen given for five years has been shown to reduce the risk of recurrence by 47% and the risk of death by 26% (1). Although tamoxifen is generally well tolerated, the use of this agent is associated with gynecologic complications such as endometrial abnormalities in postmenopausal women. An increased incidence of endometrial cancer has been reported in association with tamoxifen treatment, and the level of risk seems to be time dependent and dose dependent. Many studies have found a two to four times higher relative risk of developing endometrial cancer in women taking tamoxifen than in an age-matched population. Other side effect related to the estrogenic properties of tamoxifen includes an increased risk of thromboembolic disorders, especially when given in combination with chemotherapy (2;3) .

Aromatase Inhibitors

Aromatase inhibitors act systemically to inhibit estrogen synthesis in a variety of tissues. They prevent estrogen biosynthesis by inhibiting the enzyme aromatase, which catalyzes the conversion of androgens to estrogen. For several years there has been interest in developing inhibitors as potential therapies for hormone-responsive breast cancer in postmenopausal women.

Aminoglutethimide was the first generation aromatase inhibitor. Although effective as an adjuvant therapy in breast cancer (4;5), it was poorly tolerated and efforts to develop a better tolerated second-generation aromatase inhibitors resulted in the development of 4-OH androstenedione (formestane). However, because this compound suppressed plasma estradiol to only 1/3 of baseline levels and required parental administration it has limited clinical utility.
Subsequently, third generation aromatase inhibitors (AIs) were developed. These fell into two principal categories: a) non steroidal aromatase inhibitors, exemplified by fadrazole, vorozole, letrozole, and anastrozole, and b) steroidal aromatase inhibitors, exemplified by exemestane. All these drugs have become available for use in postmenopausal women with advanced, hormone responsive breast cancer.
Exemestane and formestane are classified as type 1 AIs on the basis of their steroidal nature and irreversible binding to the aromatase enzyme, causing permanent inactivation even after the drug is cleared from the circulation. By contrast, anastrozole and letrozole are classified as Type II AIs because they competitively inhibit the conversion of androgens to estrogens. This class of drug also includes Fadrazole, which is available only in Japan.

Anastrozole

Anastrozole (Arimidex), which became available in 1995, is a potent, orally active, highly selective non steroidal aromatase inhibitor. For second line agents in the treatment of postmenopausal women with advanced breast carcinoma, it has been shown that anastrozole offers significant benefits in survival respect to the progestin megestrol acetate (MA) (6;7).
Anastrozole increased the median survival (27 months vs. 23 months) ($P<0.025$) and the proportion of patients surviving for 2 years (56% vs.46%) compared with MA at 31 months of follow up (8)
The place of tamoxifen as golden standard for the first line treatment of postmenopausal women with advanced breast carcinoma has been challenged by the newer generation AIs. In one phase III study in which 88.4% of patients (n=312 of 353 patients) had estrogen receptor and or progesterone receptor positive tumors there was a significant increase of TTP in the anastrozole arm compared with the tamoxifen arm (anastrozole vs. tamoxifen: 11.1 months vs. 5.6 months for anastrozole vs. tamoxifen hazard ratio [HR], 1.44 lower one sided 95% confidence interval [95%CI], 1,16; p=0.0005)(9;10). Indeed, anastrozole was the first endocrine agent to show significant benefit over tamoxifen with respect to TTP in patients with hormone sensitive tumors (HR 1.13; lower one-sided 95% CL, 1.00; P=0.022 and P<0.005 (11); HR 0.77 95% confidence interval [95%CI] 0.56-0.91; p=0.047(12).

Letrozole

Letrozole is a potent, orally active, third generation aromatase inhibitor. In postmenopausal women with metastatic breast cancer a phase III study of second line therapy with letrozole (0.5 mg and 2.5 mg), showed that the clinically approved dose (2.5 mg daily) had a superior objective response (OR) rate(24% vs 16%), duration of response, time to treatment failure (5.1 vs 3.9 months) and tolerability compared with MA. (13). Buzdar and coll. reported that the 0,5 mg dose of letrozole was significantly superior to MA with respect to TTP (p 0.044) and TTF (p 0.018). (14)
As first line treatment for advanced disease, letrozole is superior to tamoxifen. In a large trial involving 907 women letrozole resulted in more tumor regression and was associated with a longer time to disease progression than tamoxifen (9.4 vs 6.0 months p= 0.0001) (15)

Exemestane

As second line agent in postmenopausal women with metastatic breast cancer, exemestane has been shown to offer significant benefit with respect to survival when compared with the progestin megestrol acetate. In a study by Kaufmann et al. treatment with exemestane produced a greater time to progression (TTP) (4.6 vs 3.9 months) and was associated with significant survival advantage in comparison with MA.(16)
The update of a small open label phase II study of exemestane vs tamoxifen as first line therapy for advanced breast cancer, showed a benefit in terms of OR rate for exemestane (45% vs 14%)(17). Those promising results were confirmed in a phase III study of similar design showing an improvement in terms of PFS in the exemestane arm.(18)

Six randomized trials have been published, that studied the efficacy of third generation aromatase inhibitors (AIs) as adjuvant treatment for postmenopausal patients with endocrine-responsive early breast cancer. Two tables summarizing characteristics and results of such trials are reported as **Annex 1 and 2**. All these trials had disease-free survival (DFS) as the primary end-point, although there were differences in its definition, and all found a significant advantage for AIs. However, there were more important differences in strategies of use of AI's, related to the timing of their administration.

Upfront strategy
Two trials compared 5-yr AIs with tamoxifen as upfront strategy; in the ATAC study with 6241 patients (19;20), there was a 0.87 hazard ratio [HR] (95% confidence interval [CI]: 0.78-0.97) favouring anastrozole; in the BIG-1 98 study with 8010 patients (21), a 0.81 HR (95% CI: 0.70-0.93) was found in favour of letrozole.

Sequential strategy
Apparently better results were obtained in three trials studying the sequential strategy . In these trials after 2-3 yrs of tamoxifen, 2-3 yrs AIs were compared to 2-3 years tamoxifen; in the IES study with 4742 patients (22), exemestane resulted effective with a 0.68 HR (95% CI: 0.56-0.82); in a combined analysis of ARNO-95 and ABCSG-8 trials with 3224 patients analyzed out of 4960 originally randomized (23), results were favourable for anastrozole with a HR of 0.60 (95% CI: 0.44-0.81); the same drug was also effective in the smaller ITA trial with 448 patients (24) with a 0.35 HR (95% CI: 0.20-0.63).

Extended adjuvant
One trial, the MA.17, explored the extension of adjuvant treatment beyond the widely accepted 5-year duration, comparing letrozole with placebo in 5.187 women who had previously received tamoxifen for 5 years (25;26); also in this trial DFS was better for letrozole, with a HR of 0.58 (95% CI: 0.45-0.76). This trial, although adding evidence in favour of sequential strategy, is not specifically relevant for the questions addressed in the present proposal.

Overall, toxicity of AIs was mild in all of the above reported adjuvant studies. As compared to tamoxifen, all AIs reduce risk of venous thromboembolism and stroke, vaginal bleeding and endometrial cancer; all AIs cause artrhalgia, bone pain, osteoporosis and increase the risk of fractures. With all AIs, but particularly with letrozole compared with tamoxifen, a higher risk of cardiac events (including myocardial infarction, ischemia and other disturbances) was observed. With anastrozole, nausea, gastrointestinal disorders and lipid metabolism disorders were reported. Quality of life analysis, available for the ATAC study (27), shows that positive gynecologic effects of anastrozole compared with tamoxifen, are paralleled by loss of libido, vaginal dryness and pain or discomfort during intercourse. Similar analyses presented by Fallowfield at the SanAntonio meeting in 2004 for the IES trial, suggest that such negative effects could be less relevant with exemestane.
In summary, as for efficacy, the upfront strategy has the advantage that the DFS benefit is already obtained during the first two years of treatment; however, the sequential strategy offers the opportunity to have a greater effect of AIs given sequentially after tamoxifen, possibly due to lower induction of drug-resistant phenotypes. The uncertainty as to which strategy is more effective has relevant clinical and economical implications, as reflected in the recent literature by several publications reporting simulations and modelling approaches; although applied on the same data, different studies produced conflicting results, favouring either the sequential (28) or the upfront strategy (29). Computer

modelling, far from being a substitute for prospective trials, strengthens the need for a properly designed randomized clinical trial.

As for toxicity, the balance prevalently favours the sequential strategy, at least for bone and heart effects, being only uterine side effects lower with upfront AIs. Costs are much lower with the sequential strategy.

The FATA study will answer an important question for the scientific community regarding the optimal strategy of hormonal treatment, with consequences on efficacy, toxicity and cost of treatment. In addition, it is the only trial to directly compare the three AIS, used both upfront or in the sequential strategy. Few ongoing trials partially address the same questions: the BIG-1 98 study is comparing upfront and sequential strategies, but only with letrozole, and a Canadian trial is comparing anastrozole with exemestane, but only in the upfront strategy. In addition, the design of FATA provides a unique opportunity for sub-protocols on gene-profiling, that should allow tailored treatments, choosing the right drug or strategy on the basis of genetic signatures of the primary breast tumor and genetic polymorphism of the patient. Also, FATA is a unique opportunity to compare drugs in terms of their impact on quality of life and sexuality, that can significantly affect patients' preferences.

On the basis of the presently available knowledge, regulatory agencies cannot express preferences among anastrozole, exemestane and letrozole, nor can they suggest any strategy (upfront or sequential) for their use, based on possible differences in efficacy or toxicity. For obvious market reasons, the most advantageous strategy for pharmaceutical companies is the complete replacement of tamoxifen with upfront AIs. However, until it is not demonstrated that the upfront strategy is more effective than the sequential one, the latter is probably convenient in terms of side effects and costs representing the best buy for the national health system (NHS). For instance, based on the 2005 Italian formulary, one day of treatment with tamoxifen (20 mg/day) costs less than 0.5 Euros, one day of treatment with any of the three AIs costs more than 6 Euros, with a ratio of about 12 to 1. Based on these estimates, 5 years of treatment with upfront AIs cost about 11000 Euros, while a sequential treatment with 2-yrs tamoxifen followed by 3-yrs AIs costs about 6900 Euros with a cost-saving of about 37%. Considering that the FATA study aims to enrol 2500 patients per year who are potentially candidate to upfront AIs in clinical practice, a notable cost-saving for the NHS will start immediately at the beginning of the study.

Objectives of the study

The study addresses two primary comparisons in postmenopausal early breast cancer patients candidate to an endocrine adjuvant treatment:

1. Sequential (tamoxifen 2 yrs →AIs 3yrs) vs upfront (AIs 5yrs) strategy of treatment
2. Anastrozole vs exemestane vs letrozole

For both comparisons, the primary end-point will be disease-free survival (DFS-DCIS) defined as the time elapsed from randomization to the first among the following events:

- local recurrence of disease
- regional recurrence of disease
- distant recurrence of disease
- contralateral invasive or intraductal breast cancer
- second primary malignancy other than breast
- death for any cause.

Study design

Type of study. Large scale, pragmatic, multicenter, open-label, phase 3 randomised trial based on a 3x2 factorial design (**Table 1**).

Arm A Anastrozole x 5 yrs	**Arm D** Tamoxifen x 2 yrs → Anastrozole x 3 yrs
Arm B Exemestane x 5 yrs	**Arm E** Tamoxifen x 2 yrs → Exemestane x 3 yrs
Arm C Letrozole x 5 yrs	**Arm F** Tamoxifen x 2 yrs → Letrozole x 3 yrs

Table 1: Study design

The study is performed according to the Italian law on non profit clinical trials (DM 17/12/2004 - GURI 22/2/2005). The study is proposed by academic researchers and supported by a grant of Italian Drug Agency (study code FARM5K3MEE).

Allocation of subjects

Patients will be equally allocated to one of the 6 study arms by centralized randomization with a computerized minimization procedure that will use ER/PgR status (both positive, one positive and one negative, one positive and one unknown), HER-2 status (positive [3+ or FISH-positive], negative, unknown), previous chemotherapy (none, adjuvant, neoadjuvant or both), and pN (pN0, pN1, pN2 or pN3) as stratification variables.

Primary Endpoint

The primary study endpoint is Disease Free Survival (DFS-DCIS), defined according to the STEEP system (Hudis et al. J Clin Oncol 2007; 25:2127-2132) as the time from randomization to the occurrence of the first among the following events:

- local recurrence of disease
- regional recurrence of disease
- distant recurrence of disease
- contralateral invasive or intraductal breast cancer
- second primary malignancy other than breast
- death for any cause.

Patients lost to follow-up or alive without any of the above at the last follow-up examination will be censored at the last follow-up examination. Occurrence of locoregional recurrence, distant metastasis, contralateral breast cancer or second invasive non-breast cancer will be ascertained through follow-up procedures detailed in **Table 2** and **Appendix 4.**

Information on death (with or without breast cancer) will be sought through periodical recall of patients not presenting at planned follow-up visits, or after 10 years of active follow-up.

In a set of exploratory analyses, the homogeneity of the comparative effects of the 3 study drugs and of the two treatment strategies across different subgroups identified on the basis of major prognostic factors (age category, tumor size, nodal status, grading, combined ER and PgR status, HER2 status, previous chemotherapy) will be evaluated as well.

Secondary Endpoints

- Overall Survival, defined as the time from randomization to death from any cause
- All the outcomes defined within the STEEP systems (i.e. IDFS, DDFS, DRFS, RFS, recurrrence-free interval, breast cancer-free interval, distant recurrence-free interval – see the table below)
- Effects on lipid profile (haematological lipid profile evaluated at each visit)

Toxicity coded according to CTCAE (Common Terminology Criteria for Adverse Events of National Cancer Institute v.3.0 – available at http://ctep.info.nih.gov/reporting/ctcnew.html. Data on toxicity will be collected at follow-up visits until the one planned at month 60.

Selection of patients

Inclusion criteria

- Women with histological diagnosis of invasive breast cancer completely removed by surgery, any T, any N.
- Postmenopausal status defined by at least one of the following conditions:
    1. Aged ≥ 60
    2. Aged 45-59 and satisfying one or more of the following criteria
        - amenorrhea for ≥12 months and intact uterus;
        - amenorrhea for <12 months and FSH within the postmenopausal range, including:
            - pts with hysterectomy
            - pts who have received HRT
            - pts with chemotherapy-induced amenorrhea
    3. bilateral oophorectomy at any age >18 years.
- Primary tumor positive for ER or PgR (≥10% tumor cells positive by immunohistochemistry or ≥ 10 fmol/mg cytosol protein by ligand binding assay).
- Adjuvant/ neoadjuvant chemotherapy, if given, must be completed before enrolment.
- Patients with HER-2 positive tumors are eligible provided that they receive trastuzumab according to registered schedule.
- Signed informed consent.

Exclusion criteria

- HRT concurrent or assumed during the month before randomization
- Recurrent or metastatic disease
- HER-2 positive tumors if treatment with trastuzumab is not feasible
- Concurrent illness that contraindicate adjuvant endocrine treatment
- Patients who have received TAM as part of any breast cancer prevention trial
- Previous history of invasive breast cancer or other invasive malignancy within the previous 10 years, other than squamous or basal cell carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied
- Concomitant severe disease which would place the patient at unusual risk
- Concurrent treatment with other experimental drugs
- Patients treated with systemic investigational drugs within the past 30 days

Treatment

Study drugs

- Anastrozole (1 mg tablets) or exemestane (25 mg tablets) or letrozole (2.5 mg tablets), once daily, for 5 years
- Tamoxifen (20 mg tablets) once daily for 2 years followed by anastrozole (1 mg tablets) or exemestane (25 mg tablets) or letrozole (2.5 mg tablets), once daily, for 3 years

All study drugs are already included in the Italian national formulary and reimbursed by the National Health System.

Interruption or discontinuation of treatment

Treatment may be temporarily suspended because of side-effects or other intercurrent reasons. The length of treatment interruption is not limited *a priori* but it is advised it to be as short as possible.

In case treatment cannot be resumed with the assigned drug, rules below should be followed:

- if the patient is receiving tamoxifen she can anticipate the aromatase inhibitor that had been assigned by randomization; clear explanation must be given for justifying anticipated treatment change.
- if the patient is receiving an aromatase inhibitor she can only receive tamoxifen as alternative treatment;
- change from an aromatase inhibitor to a different one is never permitted.

Patients may stop protocol treatment in any of the following circumstances:

- Medical reasons detrimental for patient's health and deemed reasonable by investigators
- Unacceptable toxicity
- Patient withdrawal
- Disease recurrence

Patients may withdraw at any time, for any reason, or they may be discontinued by the investigator if necessary to protect their health or the integrity of the study.

Other treatments

- Locoregional radiotherapy. If indicated according to standard guidelines, can be given either before or after randomization, also concurrently with study drugs
- Trastuzumab. Patients with HER-2 positive tumors must receive trastuzumab according to accepted schedule and indication.
- HRT. Hormone replacement therapy is prohibited.
- Biphosphonates are not allowed to prevent osteoporosis, but can be prescribed to treat it if indicated according to current practice

Toxicity

Evaluation scale

The toxicity of the treatment and the adverse events are coded according to the current NCI Common Terminology Criteria for Adverse Events (CTC-AE version 3.0) on a five-point scale (Grade 1 to 5) (Appendix III; see also: http://ctep.cancer.gov/reporting/ctc.html) and reported in detail on the digital CRF.

For events not listed in the NCI/NIH CTCAE v3.0, please use the following severity grading codes:

Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life-threatening
Grade 5	Death

Tests to be used and schedule

A complete list of tests and examinations to be performed prior to study treatment and at specified time is reported in appendix IV.

Safety

Adverse Events (AE)

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An Adverse Event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. Pre-existing conditions which worsen during a study are to be reported as Adverse Events. For the purposes of this study, occurrence of recurrence or metastasis or death due to breast cancer are not considered an adverse event, while the occurrence of a contralateral breast cancer or second cancer other than breast must be reported.

Occurrence and severity of AEs will be compared considering the patients belonging to the different arms of the study. Particularly, a comparison will be carried out between patients receiving sequential Tamoxifen and AIs vs upfront AIs. Furthermore, occurrence and severity of AEs for pts receiving the different AIs used in the study (Anastrozole vs Exemestane vs Letrozole) will be analysed. To this aim appropriate digital forms will be filled up by the physician using the study Web-based system at scheduled follow up visit. For serious suddenly occurring adverse events a different form will be filled up for each patient (see below: Serious Adverse Events). Evaluation of adverse events will be performed at each scheduled visit so that a continuous monitoring of the toxicity of the treatments will be performed.

All clinical adverse events (AEs) encountered during the clinical study will be reported on the AE page of the CRF (see also above: Toxicity). Intensity of adverse events will be graded according to the current NCI Common Terminology Criteria for Adverse Events (CTC-AE version 3.0) on a five-point scale (Grade 1 to 5) (Appendix III, see also: http://ctep.cancer.gov/reporting/ctc.html) and reported in detail on the digital CRF.

For events not listed in the NCI/NIH CTCAE v3.0, please use the following severity grading codes:

Grade 1	Mild
Grade 2	Moderate
Grade 3	Severe
Grade 4	Life-threatening
Grade 5	Death

Serious Adverse Events (SAE)

A serious adverse event is defined as any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any Adverse Event that fulfils at least one of the following criteria:

- is fatal (results in death);
- is life-threatening;
- requires in-patient hospitalization or prolongation of existing hospitalization;

- results in persistent or significant disability/incapacity;
- is medically significant or requires intervention to prevent one or other of the outcomes listed above;
- produces withdrawal of the patient from the study for causes independent of breast cancer.

All serious adverse events occurring during the study treatment period or within 30 days following the last drug administration must be reported according to the procedure described below. Any late SAE (occurring after this 30 days period) possibly or probably related to the study treatment should follow the same reporting procedure.

Relationship between drugs and SAE

The causality relationship of study drug to the adverse event will be assessed by the investigator as either Yes or No.

If there is any reasonable suspected causal relationship to the study medication, i.e. there are facts (evidence) or arguments to suggest a causal relationship, drug-SAE relationship should be assessed as Yes.

The following criteria should be considered in order to assess Yes:

- Reasonable temporal association with drug administration
- Known response pattern to suspected drug
- Disappears or decreases on cessation or reduction in dose
- Reappears on rechallenge

The following criteria should be considered in order to assess NO:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It may readily have been produced by the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known pattern of response to the suspected drug.
- It does not reappear or worsen when the drug is readministered.

Reporting of SAEs

Serious adverse events must be communicated within one working day (24 hours) of knowledge (expedited reporting) by filling-up the appropriate digital Serious Adverse Event Report Form (SAERF) onto the web-based system for data collection.

The AERF is to be completed in English and the relationship of the SAE to the study treatment reported.

After completing the digital SAERF, a hardcopy must be printed out, signed and faxed to the responsible for pharmacovigilance of the trial:

Prof. Gianfranco Di Renzo
Servizio di Farmacovigilanza
Azienda Ospedaliera Universitaria Federico II
Tel: 081-7463317

Fax: 081-7463323
e-mail: gianfranco.direnzo@unina.it

Reports of SAEs will be forwarded to due authorities.

Follow-up information is sent as a new serious SAERF, stating that this is a follow-up to the previously reported serious adverse event and giving the date of the original report. Each re-occurrence, complication or progression of the original event should be reported as a follow-up to that event. The follow-up information should describe whether the event has resolved or continues, if and how it was treated and whether the patient continued or discontinued study participation.

Withdrawal from the study and therapeutic measures shall be at the discretion of the investigator. A full explanation for the discontinuation from the study will be made on the appropriate case report form. All adverse events, regardless of severity, will be followed up by the investigator until satisfactory resolution.

The investigator and persons in charge of patient care should institute any supplementary investigations of major adverse events based on their clinical judgment of the likely causative factors. This may include seeking a further opinion from a specialist in the field of the adverse event. The Sponsor may suggest special tests based on expert advice. If a patient dies, any post-mortem findings, including histopathology, must be provided to the Sponsor.

All other minor adverse reactions will be collected on the CRF during the study.

Death on Study

Any death occurring between the randomization and 30 days following the last study drug administration must be reported to the Sponsor within 24 hours, as a **Serious Adverse Event (SAE)**, regardless of the relation to study drug(s). Deaths occurring during the study follow-up period (i.e. later than 30 days after the last infusion) need only to be reported as serious adverse event if it is thought that there is a possible relation to the study drug(s) (possible, probable). All death should be reported on the death report form section of the CRF regardless of cause.

Efficacy Evaluations

According to the STEEP system (Hudis et al. J Clin Oncol 2007; 25:2127-2132) the primary outcome indicator will be the so called DFS-DCIS, defined as time elapsing between the date of randomization and the date of one of the following events, whichever occurs first

- Local Recurrence of disease
- Regional recurrence of disease
- Distant recurrence of disease
- Contralateral invasive or intraductal breast cancer
- Second primary malignancy other than breast
- Death for any cause

Local recurrence

Local recurrence is defined as the evidence of tumor, either invasive or intraductal, in the breast surgical scar, ipsilateral breast (if breast conserving surgery was performed), ipsilateral anterior chest wall, skin or soft tissues within the local area (if mastectomy was performed). Histologic or cytologic proof is preferred.

Regional recurrence

Regional recurrence is defined as the evidence of tumor in the axillary scar, ipsilateral nodal areas (axillary, internal mammary, infraclavicular and supraclavicular) as well as the skin or soft tissues within the regional area. Histologic or cytologic proof is preferred.

Distant recurrence

Distant recurrence is defined as the evidence of tumor beyond the local-regional level as previously defined.

This includes the following:

- lymph nodes not included in the areas defined above
- skin (not included in the areas defined above)
- liver
- lung
- bone (Positive bone scans must be correlated with bone X-ray or CT /NMR bone)
- central nervous system
- other sites not defined above

Histologic or cytologic proof is preferred especially in solitary lesions.

In case of multiple pulmonary nodules on chest X-ray, multiple liver nodules on liver ultrasound or CT-scan, multiple bone lesions or multiple hot spots on the bone scan there is no need for histologic or cytologic confirmation.

Contralateral breast cancer

Contralateral breast cancer is defined as the metacronous appearance of tumor, either invasive or intraductal, in the contralateral breast.

Second Primary Malignancy other than breast

This includes any histopathologically proven invasive non-breast cancer. Excluded are non-melanoma skin cancer.

Secondary efficacy markers will be:

- the Overall Survival (OS) defined as time elapsing between the date of randomization and the date of death for any cause
- all the other outcomes defined within the STEEP system (i.e. IDFS, DDFS, DRFS, RFS, Recurrence-free interval, Breast cancer-free interval, Distant recurrence-free interval – see the table below).

Table 2. Proposed Standardized Definitions for Breast Cancer Clinical Trial End Points in the Adjuvant Setting

End Point	Invasive Ipsilateral Breast Tumor Recurrence	Local/Regional Invasive Recurrence	Distant Recurrence*	Death From Breast Cancer	Death From Nonbreast Cancer Cause	Death From Unknown Cause	Invasive Contralateral Breast Cancer†	Ipsilateral DCIS	Contralateral DCIS	Second Primary Invasive Cancer (nonbreast)‡
OS				X	X	X				
DFS-DCIS	X	X	X	X	X	X	X	X	X	X
IDFS	X	X	X	X	X	X	X			X
DDFS			X	X	X	X				X
DRFS			X	X	X	X				
RFS	X	X	X	X	X	X				
Recurrence-free interval§	X	X	X	X						
Breast cancer-free interval	X	X	X	X			X	X	X	
Distant recurrence-free interval			X	X						

NOTE: Lobular carcinoma in situ is not included as an event in these definitions as is it not generally considered to be a direct precursor of breast cancer.
Abbreviations: DCIS, ductal carcinoma in situ; OS, overall survival; DFS-DCIS, disease-free survival-ductal carcinoma in situ; IDFS, invasive disease-free survival-invasive; DDFS, distant disease-free survival; DRFS, distant relapse-free survival; RFS, recurrence-free survival.
*Site of first metastasis also should be reported, using the appropriate common data element term.
†The term "contralateral invasive breast cancer" is preferred to "second primary breast cancer," as it is less ambiguous. Ipsilateral invasive breast cancers are presumed to be a recurrence.
‡Second nonbreast primary cancers should not include squamous or basal cell skin cancers, or new in situ carcinomas of any site.
§"Interval" signifies time from random assignment or registration to event.

Trial organization
The study will be proposed to 110 Institutions actually participating in intergroup trials of the Gruppo Italiano Mammella (GIM, comprising several Italian cooperative groups, e.g. GISCAD, GOCSI, GOIM, GOIRC, GOL, GONO, GOV) and to other groups and Institutions not yet involved in such network. No particular skill is required for participation and all medical oncology units will have the opportunity to join the study, once due approvals (ethical and administrative) are obtained. The participation of about 150 centres is foreseen.

Randomization procedures and data collection will be automated on a web-based system, under the responsibility of the Data Coordinating Centre.

The study organization is structured as follows:

- a Steering Committee, chaired by the PI, including representatives of major participating groups and institutions
- a Data Coordinating Committee, chaired by the responsible of the Data coordinating centre (Clinical Trials Unit at the National Cancer Institute of Naples), including the responsible of monitoring (Lab of clinical research in oncology, IRFMN Milan) and other participants with specific skills in practical coordination of multicenter clinical trials
- a Statistical Analysis Committee: chaired by the responsible of the Statistical coordinating centre (Medical Statistics, Second University of Naples), including head biostatisticians of the Units involved in the study
- an Independent Data Monitoring Committee, to be appointed

Centralized laboratories are not planned for the main trial, and will be appointed later for specific sub-protocols.

Information retrieval.
Because of the pragmatic strategy, a reasonably low number of data will be collected for the whole study, while more specific data will be collected for sub-protocols. Data collection will be electronic, with paper forms eventually available for centres which do not have valid internet access.
Data on the primary end-point will be gathered through follow-up procedures that are consistent with current clinical practice. The follow-up scheme is summarized in **Table 2.**
From a methodological point of view and given the primary end-point of the study, the major potential source of bias may be the alteration of planned follow-up schedule, that could confound the assessment of timing of events considered in the DFS definition. To reduce this risk, there will be a proactive strategy of data management aimed at soliciting planned follow-up visits and avoid alterations of planned schedule. Such strategy will include automatic electronic reminders, direct phone calls, and warnings periodically posted on the basis of verification of collected data. In addition, descriptive statistics of actual timing of follow-up visits, across all the arms, will be done at regular intervals and reported within progress reports.

Monitoring of the study
Because of the pragmatic strategy, monitoring will be primarily conducted as a centralized procedure. At least one visit at each participating centre is programmed, but the frequency

will be modulated according to different accrual and to particular issues emerged during the central monitoring. At each visit, baseline data and follow-up events reported in the previous time period will be routinely checked, following a monitoring plan produced by the institution in charge of monitoring and approved by the data coordinating committee.

Statistical considerations

Sample size and interim analysis.

The sample size is primarily calculated for the upfront vs sequential strategy comparison, due to its potential impact on clinical practice**.**

The expected DFS-DCIS with the sequential treatment is adopted conservatively from the ABCSG 8 trial where 5-years RFS probability for sequential strategy at 5 years was equal to 0.944. Recognizing that ABCSG trial included patients with slightly better prognosis the estimated 5-years DFS of GIM3-FATA study is set equal to 0.90.
The minimal clinically worthwhile advantage with upfront AIs that the study should be able to detect is settled equal to 2% at 5 years following the previous considerations of toxicity and costs.

Thus, the main efficacy analysis is planned to identify an absolute 2% difference of DFS-DCIS at 5 years (corresponding to a HR of 0.7914), assuming a 5-yr DFS-DCIS probability in the sequential arm of 0.90, a 2-sided significance level of 0.05, power of 0.80 and three interim analysis, only planned to reject the alternative hypothesis according to a beta-spending function with Pocock boundary (futility analysis).
A maximum of 669 events are required (EAST 5 software); the interim analyses will be performed when about 268 (40%), 402 (60%) and 535 (80%) events are observed.

Applying the same absolute 2% difference of DFS-DCIS at 5 years and the same HR of 0.7914, 792 events would be required for the log-rank comparison of the three AIs, according to the Ahnn and Anderson approach (14) to have a power of 0.80 and a significance level of 0.05. Comparison of AIs will first be performed only when the result of the primary comparison will be conclusive, either at the end of the study or at an interim analysis. With the required maximum of 669 events the three-arm comparison has a power of 0.725 (14).

Assuming a recruitment rate of 1200 subjects per year 3.600 subjects should be recruited in 3 years of recruitment. Results of interim analyses will be unblinded only to IDMC. In case of 'stopping' for futility, results will be reported, but follow up will continue as planned (no treatment shift is needed, indeed) and treatment effect on overall survival would be eventually assessed without dilution.

6-months progress reports will be provided for the first 4 years, then yearly reports will be given.

Statistical analysis

All statistical analyses will be based on an intention-to-treat strategy.
CONSORT rules (15) will be applied to describe study flow and protocol deviations.
According to study design, analyses will be conducted separately (and at different times given the different number of events that are required) for the two questions.

Curves will be drawn with the Kaplan-Meier method. Statistical significance of differences will be tested by a multivariable Cox's model including stratification variables and categories of centre as covariates. Proportionality assumption will be checked by entering a time-dependent covariate of treatment by log(time) interaction. First order interactions

between treatment and stratification variables will be tested. HR and 95% CI will also be calculated for subgroup categories of stratification variables and depicted as Forest plot.

According to study design, three interim analysis, only planned to reject the alternative hypothesis according to a beta-spending function with Pocock boundary (futility analysis) will be performed when about 268 (40%), 402 (60%) and 535 (80%) events are observed for the comparison of the two strategies.

As for the comparison of the three AIs, global null hypothesis of treatment equivalence will be first tested by log-rank test; if the overall comparison will be significant, pairwise comparisons between AIs will be performed with Bonferroni-Holm adjustment.

As for toxicity analyses, for each patient and for each type of toxicity, the worst degree ever suffered will be used for the analysis.

In the comparison between strategies, the whole pattern of toxicity (all grades) will be considered for each item; analysis will be done by a linear rank test with significance level set at 0.01.

In the comparison of the three AIs, global null hypothesis of treatment equivalence will be first tested by nonparametric ANOVA at 0.01 level; if the overall comparison will be significant, pairwise comparisons between AIs will be done by a linear rank test with Bonferroni-Holm adjustment.

Ethical aspects.
All interventions (both diagnostic and therapeutic) planned in this study strictly overlap with current clinical practice in Italy. Such condition should not change during next years, when a wide diffusion of AIs as adjuvant treatment of early breast cancer is foreseeable. Thus, potential risks for patients enrolled in the FATA study are similar to those of patients treated in a clinical practice setting. These include the possibility of suffering an adverse event or the possibility of suffering a recurrence of the disease. Both these risks are quite low, being the study treatments only fairly toxic and the population on study extremely favourable in terms of prognosis. As for adverse events, an expedited electronic system of reporting will be set, according to European rules.

Administrative Aspects

This study is promoted by the Dipartimento di Endocrinologia ed Oncologia Molecolare e Clinica, Università Federico II, Napoli, Italy, which play the role of not-for-profit Sponsor.

The trial is being conducted in accordance with the Good Clinical Practice guidelines, with the declaration of Helsinki (see Appendix II) and with national laws and directives regarding clinical trials.

The trial is financially supported by the Italian Drug Agency (AIFA) with a grant for independent clinical researches (grant no. FARM5K3MEE). All study drugs are already included in the Italian national formulary and reimbursed by the Italian National Health System.

Data deriving from this clinical trial are not intended for drug registration nor for patent applications, but only for scientific and educational purposes, which include presentation at scientific meetings, congresses and symposia and/or publication in scientific journals. These data are the property of the Dipartimento di Endocrinologia ed Oncologia Molecolare e Clinica, Università Federico II, Napoli, Italy, which shares it with all participating researchers.

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Annex 1 . Summary tables of published phase 3 trials testing aromatase inhibitors as adjuvant treatment for postmenopausal patients with endocrine-responsive early breast cancer(design and patients characteristics, efficacy, toxicity and definition of endpoints)

Table 1. Study design and baseline characteristics of patients

Study ID (Refs.)	Type of AI	Treatment strategy and length of AIs	Comparator drug	Adjuvant endocrine treatment before trial	N. patients	Median age (yrs)	% known ER+	% tumor ≤2cm	% node-positive	% with previous chemotherapy
ATAC (1,2)	Anastrozole	Up-front, 5 yrs	Tamoxifen	None	6.241[a]	64[b]	84[c]	63	39[d]	22
BIG1-98 (3)	Letrozole	Up-front, 5 yrs [e]	Tamoxifen	None	8.010	61	98	62	41	25
IES (4)	Exemestane	Sequential, 2-3 yrs	Tamoxifen	Tamoxifen 2-3 yrs	4.742	64[b]	81	n.r.	49[d]	32
ARNO-95/ABCSG-8 (5)	Anastrozole	Sequential 2-3 yrs	Tamoxifen	Tamoxifen 2-3 yrs	3.224[f]	62	96	70	26	0
ITA (6)	Anastrozole	Sequential 2-3 yrs	Tamoxifen	Tamoxifen 2-3 yrs	448	63	89	47	100	67
MA.17 (7,8)	Letrozole	Extension, 5 yrs	Placebo	Tamoxifen 5 yrs	5.187	62	98[c]	n.r.	50[d]	46

Footnotes

[a] = ATAC also included further 3.125 assigned the combination tamoxifen + anastrozole, that are not considered in this table
[b] = Mean age
[c] = refer to either ER or PgR
[d] = including approximately 5% of cases with N status unknown
[e] = data on sequential strategy have not been reported yet
[f] = out of 4.960 originally randomized in two separate trials
n.r. = not reported

Table 2. Analysis and efficacy outcomes reported in the more recent extended publication

Study ID (Refs.)	Primary end-point	Median follow-up (months)	Primary end-point		TDM		CLBC		OAS		DWBC
			N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N	HR (95% CI)	N
ATAC (1,2)	DFS [1]	68	575/651	0.87 (0.78-0.97)	324/375	0.86 (0.74-0.99)	35/49	0.58 (0.38-0.88)	831[a]	0.97 (0.85-1.12)	331[a]
BIG1-98 (3)	DFS [2]	26	351/428	0.81 (0.70-0.93)	184/249	0.73 (0.60-0.88)	16/27	n.r.	166/192	0.86 (0.70-1.06)	55/38
IES (4)	DFS [1]	31	183/266	0.68 (0.56-0.82)	114/174	n.r.	9/20	0.44 (0.20-0.98)	93/106	0.88 (0.67-1.16)	39/39
ARNO-95/ABCSG-8 (5)	EFS [3]	28	67/110	0.60 (0.44-0.81)	46/75	0.61 (0.42-0.87)	12/16	n.r.	45/59	n.r.	21/28
ITA (6)	DFS [4]	36	12/32	0.35 (0.18-0.68)	10/19	0.49 (0.22-1.05)	1/2	n.r.	4/10	-	0/3
MA.17 (7,8)	DFS [3]	30	92/155	0.58 (0.45-0.76)	52/82	0.60 (0.43-0.84)	17/28	0.63 (0.18-2.21)	51/62	0.82 (0.57-1.19)	35/40

Footnotes

TDM = time to distant metastases
DFS = disease-free survival
CLBC = contralateral breast cancer
OAS = Overall survival
DWBC = Death without breast cancer
N= number of events in AI/non AI arms
HR = Hazard Ratio for AI vs comparator
CI = Confidence interval

[1] = include locoregional or distant recurrence, CLBC and DWBC as events
[2] = as [1] but also include second non-breast invasive cancer as event
[3] = include locoregional or distant recurrence, CLBC as event
[4] = include locoregional or distant recurrence as event
[a] = overall number of deaths, details by arm not reported
n.r. = not reported

APPENDIX I - World Medical Association Declaration of Helsinki
Recommendations guiding physicians in biomedical research involving human subjects

Adopted by the 18th World Medical Assembly Helsinki, Finland, June 1964 and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989 and the
48th General Assembly, Somerset West, Republic of South Africa, October 1996

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

The Declaration of Geneva of the World Medical Association binds the physician with the words, "The Health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I. BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.
2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given his or her consent.
4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.
5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.
6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.
8 In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.
9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.
10. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.
11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.
12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (Clinical Research)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.
2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient - including those of a control group, if any - should be assured of the best proven diagnostic and therapeutic method. This does not exclude the use of inert placebo in studies where no proven diagnostic or therapeutic method exists.
4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.
5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee (I, 2).
6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subject should be volunteers - either healthy persons or patients for whom the experimental design is not related to the patient's illness.
3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.
4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

APPENDIX II – Performance Status

KARNOFSKY	SCALE	ECOG/WHO	SCALE
Normal, no complains	**100**	Able to carry out all normal activity without restriction	**0**
Able to carry on normal activities. Minor sign and symptoms of disease Normal activity with effort	**90** **80**	Restricted in physically strenuous activity but ambulatory and able to do light work.	**1**
Cares for self. Unable to carry on normal activity or to do active work Requires occasional assistance, but able to care most of his need	**70** **60**	Ambulatory and capable of all self-care but unable to carry out any work.	**2**
Requires considerable assistance, and frequent medical care Disabled. Requires special care and assistance	**50** **40**	Up and about more than 50 % of waking hours. Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours	**3**
Severity disabled. Hospitalisation indicated though death not imminent Very sick. Hospitalisation necessary. Active supportive treatment necessary Moribund	**30** **20** **10**	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	**4**

APPENDIX III - Flow Chart of Examinations

Visit	Baseline	2	3	4	5	6	7	8	9	10	11	At recurrence or trial discontinuation before 5 yrs	Yearly until death
Trial month	0	6	12	18	24	30	36	42	48	54	60		
Informed consent	x												
Medical History/current medical conditions (1)	x												
Inclusion/ Exclusion criteria	x												
Physical examination (2)	x	x	x	x	x	x	x	x	x	x	x	x	x
Demography/ menopause	x												
Prior anticancer therapy	x												

Breast cancer surgery	x												
ECOG PS	x												
Concomitant treatments	x	x	x	x	x	x	x	x	x	x	x		
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x
Blood chemistry (3)	x*	x	x	x	x	x	x	x	x	x	x	√	√
ECG	x*		x		x		x		x		x	x	x
Mammogram	x***		x		x		x		x		x		x
Chest x ray	x**	x	x	x	x	x	x		x		x		x
Bone scan	x***		x		x		x		x		x		x
Abdominal US, CT liver	x**	x	x	x	x	x	x		x		x	x	x
Gynecologic exam	√	√	√	√	√	√	√	√	√	√	√	√	√
Survival/disease status	x	x	x	X	x	x	x	x	x	x	x		x

x = mandatory
√ = if medically indicated
1 includes relevant non malignant disease
2 includes weight and height
3Includes creatinine, AST, ALT, total bilirubin, alkaline phosphatase, calcium, total and HDL cholesterol
* within 1 month from randomization
** within 3 months from randomization
*** within 1 year from randomization

Appendix IV- Consenso Informato e lettera al Medico Curante

Foglio Informativo per la paziente e Consenso Informato

Titolo dello studio: FATA – First Adjuvant Trial on All aromatase inhibitors in early breast cancer. Studio di fase III di confronto tra anastrozolo, letrozolo ed exemestane e tra strategia sequenziale (2 anni di terapia con tamoxifen seguiti da 3 anni di terapia con inibitori delle aromatasi) verso strategia *up-front* (5 anni di terapia con inibitori delle aromatasi) nel trattamento adiuvante del carcinoma mammario ormono-responsivo

Gentile Signora,
in questo centro si sta svolgendo uno studio clinico il cui scopo è valutare quale sia il migliore tra 6 diversi trattamenti ormonali per le donne in menopausa che hanno subito un intervento chirurgico per un tumore della mammella e che necessitano di ormonoterapia adiuvante. **Tutti i farmaci utilizzati in questo studio sono già autorizzati dal Ministero della Salute per il trattamento del tumore della mammella in donne in menopausa.**
Con questo documento desideriamo spiegarLe quali sono i motivi per cui riteniamo che Lei possa partecipare a questo studio e cosa dovrà fare qualora decidesse di partecipare.
Il medico responsabile dello studio è a Sua disposizione per rispondere a tutte le domande che riterrà di porre qualora qualche punto Le risultasse poco chiaro. La preghiamo di leggere attentamente questo documento e di prendersi tutto il tempo necessario per decidere, in assoluta libertà, se partecipare a questo studio.

Scopo dello Studio

La maggior parte dei tumori della mammella dipendono per la loro crescita dagli ormoni femminili (estrogeni). Una strategia terapeutica che si è rivelata efficace negli anni per bloccare la crescita del tumore è la terapia con farmaci anti-estrogeni.
Il tamoxifene è un anti-estrogeno che, utilizzato per un periodo di 5 anni dopo l'intervento chirurgico, è stato considerato il trattamento standard per le donne affette da tumore della mammella fino a qualche anno fa. Una nuova classe di farmaci anti-ormonali, gli inibitori dell'aromatasi di terza generazione (anastrozolo. letrozolo, exemestano) hanno, negli ultimi anni, dimostrato una superiorità rispetto al tamoxifene nel trattamento delle donne in menopausa con tumore della mammella e sono, quindi, diventati un nuovo punto di riferimento nel trattamento di questa patologia. In uno studio clinico internazionale è stato dimostrato che il trattamento per 5 anni con l'inibitore dell'aromatasi anastrozolo è più efficace nel ridurre il rischio di ricaduta dopo intervento chirurgico rispetto al trattamento con tamoxifen per 5 anni. Diversi studi hanno dimostrato, inoltre, che il trattamento con uno dei tre inibitori dell'aromatasi per 2 o 3 anni dopo 2 o 3 anni di trattamento con tamoxifene è più efficace nel ridurre il rischio di ricaduta dopo intervento chirurgico rispetto al trattamento con tamoxifen per 5 anni. Attualmente, quindi, sappiamo che un trattamento farmacologico contenente un inibitore dell'aromatasi è più efficace del solo tamoxifene nel trattamento della Sua patologia. Quello che non è ancora chiaro dagli studi è quale sia il miglior modo di utilizzare gli inibitori dell'aromatasi: se dopo trattamento con 2 anni di tamoxifene o per 5 anni dopo l'intervento chirurgico. Inoltre non è chiaro quale sia il miglior inibitore dell'aromatasi tra i tre disponibili in commercio (anastrozolo. letrozolo, exemestano).

Obiettivo dello studio

Lo studio a cui Le proponiamo di partecipare è una ricerca nazionale che coinvolgerà circa 10000 pazienti in menopausa.
Lo studio ha l'obiettivo di valutare se il trattamento con 5 anni con un inibitore dell'aromatasi (anastrozolo. letrozolo o exemestano) sia superiore al trattamento con tamoxifene per 2 anni seguito da inibitore dell'aromatasi (anastrozolo. letrozolo, exemestano) per 3 anni. Il secondo obiettivo dello studio è quello di valutare quale sia il migliore tra i tre inibitori dell'aromatasi (anastrozolo. letrozolo, exemestano).
I possibili tipi di trattamento che Lei potrebbe ricevere nello studio sono dunque i seguenti:
1) Anastrozolo per 5 anni
2) Letrozolo per 5 anni
3) Exemestano per 5 anni
4) Tamoxifene per 2 anni seguito da Anastrozolo per 3 anni
5) Tamoxifene per 2 anni seguito da Letrozolo per 3 anni
6) Tamoxifene per 2 anni seguito da Exemestano per 3 anni
Se Lei decidesse di partecipare allo studio, il tipo di trattamento che riceverà sarà scelto attraverso un procedimento computerizzato denominato randomizzazione che assicura l'assoluta casualità della scelta. Questo significa che Lei ha le stesse possibilità di partecipare ad uno qualsiasi dei 6 bracci di trattamento.
I farmaci utilizzati in questo studio sono in assoluto i migliori nel trattamento ormonale adiuvante del carcinoma mammario ormono-responsivo e sono tutti già utilizzati nella normale pratica clinica. Pertanto, qualora decidesse di partecipare allo studio, Lei riceverebbe un ottimo trattamento adiuvante, con farmaci innovativi, qualsiasi fosse il braccio di trattamento assegnatoLe.

Effetti collaterali

Gli inibitori dell'aromatasi sono farmaci generalmente molto ben tollerati. I più comuni effetti collaterali riportati con gli inibitori dell'aromatasi sono: dolori osteo-articolari, secchezza delle mucose, vampate di calore, insonnia, cefalea, nausea, stanchezza e aumento della sudorazione.

Quali sono i possibili benefici dello studio?

E' possibile che Lei possa trarre dallo studio un beneficio diretto in quanto la terapia che Le verrà somministrata potrà contribuire a ridurre il rischio di avere una ricaduta dalla malattia. Tuttavia, Lei potrebbe non trarre alcun beneficio diretto da questo studio, ma le conoscenze che verranno acquisite anche grazie alla sua partecipazione, saranno comunque di utilità sia per Lei che per altre pazienti.

Quali sono i suoi diritti?

Partecipando a questo studio, Lei non dovrà sostenere alcuna spesa. La partecipazione a questo studio è completamente volontaria. Se Lei decide di parteciparvi Le verrà chiesto di firmare e datare il modulo di consenso informato e di trattenere per sé questo foglio informativo. Qualora dovesse decidere di partecipare allo studio, se in un secondo momento dovesse cambiare idea, potrebbe in ogni caso decidere di ritirare il suo Consenso e ritirarsi

dallo studio. Questo non influenzerebbe in alcun modo la successiva cura della sua malattia. Le verrà comunque prescritto il miglior trattamento disponibile e la sua decisione non influenzerà in alcun modo le cure che Le verranno successivamente prestate. Per questo studio La informiamo che "la copertura assicurativa è ricompressa nell'ambito di quella prevista per l'attività clinica generale o di ricerca delle strutture partecipanti " secondo quanto previsto dal DM del 17 dicembre 2004 art. 2 comma 4.
La preghiamo di informare il medico responsabile dello studio circa eventuali danni derivanti dalla ricerca e la natura delle spese da sostenere.
Firmando la parte del presente documento denominata "consenso informato scritto", Lei non perde alcun diritto legale.

Se desiderasse ulteriori informazioni su questo studio può contattare il seguente medico:

_____ telefono:_____

Confidenzialità

La sua identità sarà protetta e Lei sarà identificata tramite iniziali e un codice numerico. La informiamo che sia per le Autorità Sanitarie, sia per il promotore della sperimentazione è importante poter esaminare le cartelle cliniche originali dei pazienti allo scopo di adempiere alle normative che regolano le sperimentazioni cliniche.
I suoi dati clinici relativi allo studio saranno raccolti su apposite schede ed inviati al Centro di Coordinamento, su tali schede non apparirà il suo nome, ma un codice identificativo.
I suoi dati personali saranno conservati con estrema riservatezza ai sensi del D.L. 196 del 30/06/2003 in materia di tutela dei dati personali. I dati presenti nelle cartelle cliniche relative allo studio saranno resi disponibili dal Medico responsabile dello studio, al personale qualificato delle Autorità Sanitarie, del Promotore o di suoi delegati e dei comitati etici nel totale rispetto dei suoi diritti e senza violare la confidenzialità dei dati, nella misura consentita dai regolamenti di Legge. In ogni caso Lei avrà pieno accesso, tramite il suo medico, alle informazioni che La riguardano.

Procedure dello studio.

E' molto importante che Lei segua attentamente le istruzioni che Le verranno fornite dal Medico responsabile dello studio.
Tutti i farmaci dello studio vengono assunti per via orale con cadenza giornaliera. Lei sarà sottoposta ad una visita clinica ogni 3 mesi per i primi 3 anni e ogni 6 mesi per i successivi due anni. Dopo 5 anni il trattamento verrà sospeso e Lei continuerà a essere visitata con cadenza annuale. Le verranno richiesti periodicamente degli esami di sangue e alcuni esami strumentali come la mammografia (1 volta all'anno), la radiografia del torace (ogni 6 mesi), l'ecografia dell'addome (ogni 6 mesi) e la scintigrafia ossea (1 volta all'anno). Altri esami Le verranno richiesti, in base al suo stato di salute, a discrezione del Medico responsabile.

LA RINGRAZIAMO PER LA SUA DISPONIBILITÀ E PER IL SUO AIUTO

CONSENSO INFORMATO SCRITTO

Io sottoscritta dichiaro di accettare la proposta di partecipare allo studio clinico descritto nel documento "Foglio informativo per la paziente". Pertanto, accetto di essere sottoposta alla terapia ormonale oggetto dello studio.

Il mio consenso è espressione di una libera decisione. Sono consapevole di essere libera di ritirarmi dallo studio in qualsiasi momento e di poter esigere di essere successivamente curata con le terapia di impiego comune per il trattamento del carcinoma mammario.
Mi è stata data l'opportunità di leggere le informazioni contenute nella parte informativa e di porre domande circa gli scopi e le metodiche dello studio, i benefici e i possibili rischi, gli effetti dei farmaci in studio e di miei diritti come partecipante alla ricerca.
Esprimo il consenso anche ai sensi del D.L. 196 del 30/06/2003 in materia di tutela dei dati personali, affinché i dati presenti nelle mie cartelle cliniche relative alla studio vengano resi disponibili dal Medico responsabile dello studio alle Autorità sanitarie e dai comitati etici nel rispetto dei miei diritti.
Qualora io lo desideri, il mio Medico di famiglia, o un altro medico da me indicato, sarà informato circa la mia partecipazione a questo studio.

Nome e Cognome della Paziente

_____

Firma della Paziente Data _____

_____

Dichiarazione dello Sperimentatore

Dichiaro di aver fornito alla paziente informazioni complete e spiegazioni dettagliate circa la natura, le finalità, le procedure e la durata di questo studio. Dichiaro di aver fornito alla paziente il foglio informativo ed una copia del modulo di consenso informato datata e firmata.

Nome e Cognome del Ricercatore

_____

Firma della Ricercatore Data _____

_____

LETTERA INFORMATIVA PER IL MEDICO CURANTE

Alla cortese attenzione del

Dr.....

Egregio/a Collega,

con la presente, La informiamo che la Sua paziente la
Sig.ra.....
operata per carcinoma della mammella, sta partecipando ad uno studio clinico nazionale multicentrico dal titolo: **Studio di fase 3 di confronto tra anastrozolo, letrozolo ed exemestane e tra strategia sequenziale (2 anni di terapia con tamoxifene seguiti da 3 anni di terapia con inibitori delle aromatasi) verso strategia *up-front* (5 anni di terapia con inibitori delle aromatasi) nel trattamento adiuvante del carcinoma mammario ormono-responsivo.**

L'obiettivo principale dello studio è quello comparare la sopravvivenza libera da malattia nelle pazienti trattate con 2 anni di Tamoxifen seguiti da 3 anni di terapia con un inibitore dell'aromatasi oppure con cinque anni di terapia con inibitore dell'aromatasi.
Alla paziente verrà somministrato uno dei seguenti trattamenti ormonali adiuvanti con:

- Letrozolo per 5 anni
- Anastrozolo per 5 anni,
- Exemestane per 5 anni
- Tamoxifene per 2 anni seguito da Letrozolo per 3 anni
- Tamoxifene per 2 anni seguito da Anastrozolo per 3 anni
- Tamoxifene per 2 anni seguito da Exemestane per 3 anni

a seconda del braccio di trattamento assegnato.
Tutti i farmaci in studio sono assunti per via orale.

Mi auguro di avere con lei una stretta collaborazione per quanto riguarda lo stato di salute della paziente durante e dopo la terapia.

Rimango a Sua disposizione per ogni chiarimento.

Cordiali saluti.
Dr.....
Tel.....