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CLINICAL TRIAL

# Phase III evaluating the addition of fulvestrant (F) to anastrozole (A) as adjuvant therapy in postmenopausal women with hormone receptor-positive HER2-negative (HR+/HER2−) early breast cancer (EBC): results from the GEICAM/2006–10 study

**Manuel Ruíz-Borrego[1] · Angel Guerrero-Zotano[2] · Begoña Bermejo[3] · Manuel Ramos[4] · Josefina Cruz[5] · Jose Manuel Baena-Cañada[6] · Beatriz Cirauqui[7] · Álvaro Rodríguez-Lescure[8] · Emilio Alba[9] · Noelia Martínez-Jáñez[10] · Montserrat Muñoz[11] · Silvia Antolín[12] · Isabel Álvarez[13] · Sonia Del Barco[14] · Elena Sevillano[15] · José Ignacio Chacón[16] · Antonio Antón[17] · María José Escudero[18] · Victoria Ruiz[18] · Eva Carrasco[18] · Miguel Martín[19] on behalf of GEICAM**

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## Abstract

**Purpose** GEICAM/2006–10 compared anastrozole (A) versus fulvestrant plus anastrozole (A + F) to test the hypothesis of whether a complete oestrogen blockade is superior to aromatase inhibitors alone in breast cancer patients receiving hormone adjuvant therapy.

**Methods** Multicenter, open label, phase III study. HR+/HER2− EBC postmenopausal patients were randomized 1:1 to adjuvant A (5 years [year]) or A + F (A plus F 250 mg/4 weeks for 3 year followed by 2 year of A). Stratification factors: prior chemotherapy (yes/no); number of positive lymph nodes (0/1–3/≥ 4); HR status (both positive/one positive) and site. Primary objective: disease-free survival (DFS). Planned sample size: 2852 patients.

**Results** The study has an early stop due to the financer decision with 870 patients (437 randomized to A and 433 to A + F). Patient characteristics were well balanced. After a median follow-up of 6.24y and 111 DFS events (62 in A and 49 in A + F) the Hazard Ratio for DFS (combination vs. anastrozole) was 0.84 (95% CI 0.58–1.22; $p = 0.352$). The proportion of patients disease-free in arms A and A + F at 5 year and 7 year were 90.8% versus 91% and 83.6% versus 86.7%, respectively. Most relevant G2-4 toxicities (≥ 5% in either arm) with A versus A + F were joint pain (14.7%; 13.7%), fatigue (2.5%; 7.2%), bone pain (3%; 6.5%), hot flushes (3.5%; 5%) and muscle pain (2.8%; 5.1%).

**Conclusions** The GEICAM/2006–10 study did not show a statistically significant increase in DFS by adding adjuvant F to A, though no firm conclusions can be drawn because of the limited sample size due to the early stop of the trial. **ClinicalTrials.gov:** NCT00543127.

**Keywords** HR+/HER2− · Early breast cancer · Fulvestrant · Anastrozole · Luminal

## Introduction

Adjuvant hormone therapy has demonstrated beyond any doubt its ability in reducing distant, loco-regional and contralateral relapses in operable breast cancer expressing hormone receptors [1]. The significant reduction in the risk of recurrence achieved with the introduction of tamoxifen first, and aromatase inhibitors (AIs) later led to the prevention of thousands of deaths from breast cancer worldwide [1, 2]. Based on these data, their use is recommended in published breast cancer guidelines [3–5].

Trial results have been presented as a Proffered Paper (Oral) presentation in the European Society for Medical Oncology (ESMO) 2017.

The members of GEICAM participant investigators are listed in "Acknowledgement" section.

✉ Miguel Martín
mmartin@geicam.org

Extended author information available on the last page of the article

However, a clinically significant proportion of hormone receptor (HR)-positive breast cancer patients still suffer relapse in spite of the use of tamoxifen or AIs. New hormone therapies are then needed.

Fulvestrant, a selective oestrogen receptor-degrader (SERD) is an active hormone agent for patients with HR-positive metastatic breast cancer (MBC) [6] and has recently shown to improve progression-free survival (PFS) versus anastrozole as first-line therapy for MBC in the FALCON phase III trial [7].

In MBC, fulvestrant has been combined with anastrozole in an attempt to produce a more complete blockade of the oestrogen receptor (ER) pathway. Two studies comparing the combination of fulvestrant plus anastrozole versus anastrozole single agent in MBC have been reported, with conflicting results. In the FACT trial, the combination of anastrozole plus fulvestrant did not improve PFS versus anastrozole [8]. Conversely, an ECOG trial carried out in patients with less-extensive adjuvant therapy, showed an improvement in PFS and overall survival with the combination [9]. In addition, in the neoadjuvant setting, the combination of fulvestrant and anastrozole failed to show biomarker evidence of superior biological activity over fulvestrant alone [10]. However, in this trial, the biological effect of fulvestrant could have been underestimated since efficacy assessment was done at day 18, following a single dose of fulvestrant 500, far from the regimen approved in clinical practice.

In January 2008, before the results of these trials were made public, we started the GEICAM/2006–10 study, a randomized trial comparing anastrozole with the combination of anastrozole plus fulvestrant in patients with HR-positive operable breast cancer. We present here the results of this trial, which was prematurely stopped due to the decision of the financer based on the results of the FACT and neoadjuvant trial.

## Patients and methods

### Study design

This is a multicenter, open label, randomized, phase III trial. Eligible patients were randomly assigned in a 1:1 ratio to receive oral anastrozole (A) 1 mg daily for 5 years versus fulvestrant (F) in combination with anastrozole (same schedule). F was administered intramuscularly (IM) concurrently with A for the initial 3 years with the following schedule: 500 mg on day 1 of cycle 1, 250 mg on days 14 and 28 of cycle 1 and 250 mg on day 1 of each subsequent 28-days cycle thereafter. Randomization was centralized at the GEICAM headquarters. Patients were stratified according to prior chemotherapy (yes vs. no), number of positive lymph nodes (0 vs. 1–3 vs. ≥ 4) and HR status (both ER and progesterone receptor [PR] positive [+] vs. ER+ and PR negative [−] vs. ER− and PR+) and institution.

The primary endpoint of the study was to compare *disease-free survival (DFS)*, defined as the interval from the date of randomization to the date of local or distant invasive recurrence of breast cancer, second primary breast cancer or death from any cause, whichever occurred first. Secondary endpoints were to compare the following between both treatment arms: *time to recurrence (TtR)*, defined as the time from randomization to local or distant invasive recurrence of breast cancer; *breast cancer-specific survival (BCsS)*, defined as the time from randomization to death due to breast cancer; *overall survival (OS)*, defined as time from randomization to death from any cause and *safety and tolerability*. An additional objective was to explore the effects of adjuvant therapy on bone mineral density (BMD) and osteoporosis. Osteoporosis was defined as a score of 2.5 SD below the mean BMD of a young healthy woman (*T*-score) based on the lowest BMD either at the lumbar spine or hip.

### Eligibility criteria

Eligible patients were postmenopausal women with centrally confirmed histologic diagnosis of HR+ (ER+ and/or PgR+) and human epidermal growth factor receptor 2 (HER2)-negative early breast cancer. Postmenopausal women were defined as those either with bilateral oophorectomy, or ≥ 60 years, or ≥ 45 years with amenorrhea of at least 12 months at diagnosis (if intact uterus). If previous hysterectomy, FSH and estradiol values had to be within the local laboratory postmenopausal ranges. In patients pretreated with LH-RH analogues, the last dose should have been administered at least 6 months before randomization. Patients with operable stage I (with tumour size of > 1 cm), II, IIIA and IIIC (except patients with metastasis in infraclavicular nodes) were eligible. Patients had to have undergone surgery with curative intent followed/preceded or not by adjuvant/neoadjuvant chemotherapy. Patients were not eligible if they had any of the following criteria: current or previous malignancy other than breast cancer or nonmelanoma skin cancer or cervix carcinoma in situ treated within the 5 prior years before study entry; inadequate bone marrow, liver or renal functions; any concurrent cardiac illness or medical condition, which could affect compliance with the protocol or interpretation of results.

### Study procedures

Baseline assessments were performed within 21 days of randomization. These included physical examination, Eastern Cooperative Oncology Group (ECOG) performance status (PS), electrocardiogram (ECG), haematology, biochemistry and the following radiological tests to discard metastatic

disease: chest X-ray or CT-scan, abdominal echography or CT-scan and bone scan (only if ≥ 3 axillary nodes and/or alkaline phosphatase elevation or bone symptoms).

During adjuvant treatment, patients had physical examination, ECOG PS evaluation, blood haematology and biochemistry every 3 months for the 2 first years and every 6 months for the following 3 years. A yearly mammography was also mandatory.

To measure BMD, a densitometry (DXA) had to be performed (at the lumbar spine and hip) at baseline and then yearly for 5 years.

Adverse events were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [11]. Adverse event data were collected from randomization up to date of the last dose of study medication.

### Statistical considerations

The trial was designed to detect an increase of 3% in the 5-year DFS between the two arms (90% was expected for patients on A and 93% for patients receiving A and F) for a Hazard Ratio of 0.6888. With a power of 80% and a two-sided significance level of 0.05, 2716 patients were needed; assuming a dropout rate of 5%, 2852 patients were required to enter the study. However, recruitment was stopped early with 870 patients included, based on data available in the metastatic and neoadjuvant setting with the combination of A and F [12, 13]. With this sample size, the real study power to show the above-mentioned difference was reduced to 35.5%.

Analyses of DFS, TtR, BCsS, and OS were performed on the intent-to-treat (ITT) population, defined as all-randomized patients. Time to event variables were analysed using the Kaplan–Meier product limit estimator and an unstratified log-rank test was used to compare treatment arms. Hazard ratios and 95% confidence intervals were estimated using a Cox proportional-hazards model. All statistical tests were two-sided with a significance level of 0.05 unless stated otherwise. Safety analysis was performed on all patients who received at least one dose of therapy according to the treatment received.

To compare the evolution in BMD between treatment arms the Wilcoxon–Mann–Whitney test was used.

All analyses were performed using the Statistical Analysis System (SAS) Enterprise Guide 5.1 software (SAS Institute Inc., Cary, NC, USA).

## Results

### Patient characteristics

From January 2008 to June 2010, 870 patients were recruited in 53 Spanish sites belonging to GEICAM, Spanish Breast Cancer Group. From them, 437 were randomized to A and 433 to A plus F (A + F). Eighteen patients (3 in arm A arm and 15 in arm A + F) never received treatment, in addition three patients from arm A + F did not receive F; thus, 870 were evaluable for efficacy in an intent-to-treat basis and 852 patients (437 on A and 418 on A + F) were evaluable for safety (Fig. 1).

Patients and tumour characteristics as well as prior treatments were similar between arms (Table 1). Median age was 62 years (range 40 to 86 years), 612 patients (70.3%) had conservative surgery, 539 (62.0%) had axillary lymph-node dissection and 329 (37.8%) sentinel lymph-node biopsy. Concerning HR status, 765 tumours (87.9%) had both ER and PgR positive and 101 (11.6%) were ER positive and PgR negative. Neo/adjuvant chemotherapy was administered to 593 (68.2%) patients; 389 (65.6%) received anthracyclines plus taxanes, 135 (22.8%) anthracyclines without taxanes, 62 (10.4%) taxanes without anthracyclines and 7 (1.2%) other chemotherapies.

### Treatment exposure

Treatment with A was completed as planned by 598 patients (70.7% of A patients and 69.9% of A + F patients). Median duration of treatment was 4.96 years (range 0.04 to 5.71) and similar for both treatment arms. Median relative dose intensity was 99% in both arms.

Treatment with F for 3 years was completed as planned by 183 patients (44.1%). The proportion of patients who completed treatment with F for 2 years and 1 year were 54.5% and 82.2%, respectively. Median duration of treatment was 2.46 years (range 0 to 3) and median relative dose intensity was 81%.

### Efficacy analysis

After a median follow-up time of 6.37 years (range 0 to 8.29 years), 111 DFS events were reported, 62 in the A arm and 49 in the A + F arm (Table 2). The Hazard Ratio for relapse in the A + F versus the A arm was 0.84 (95% CI 0.58 to 1.22; $p = 0.3517$). The 5-year rates were 90.8% (95% CI 88.0% to 93.6%) for arm A patients and 91% (95% CI 88.2% to 93.9%) for arm A + F patients, (log-rank $p$ value = 0.351; Fig. 2). The 7-year DFS rates were 83.3% (95% CI 79.2% to 87.5%) and 86.9% (95% CI 83.3% to 90.6%) for arms A and A + F, respectively.

The 5-year TtR and BCsS were 92.7% for arm A and 94.0% for arm A + F patients (log-rank $p$ value = 0.406) and 97.0% for arm A and 97.1% for arm A + F patients (log-rank $p$ value = 0.966), respectively (Fig. 3a, b).

Regarding OS (Fig. 3c), we observed 62 deaths, 34 in the A arm and 28 in the A + F arm. The 5-year OS was 95.3% for arm A and 94.8% for arm A + F (log-rank $p = 0.558$).

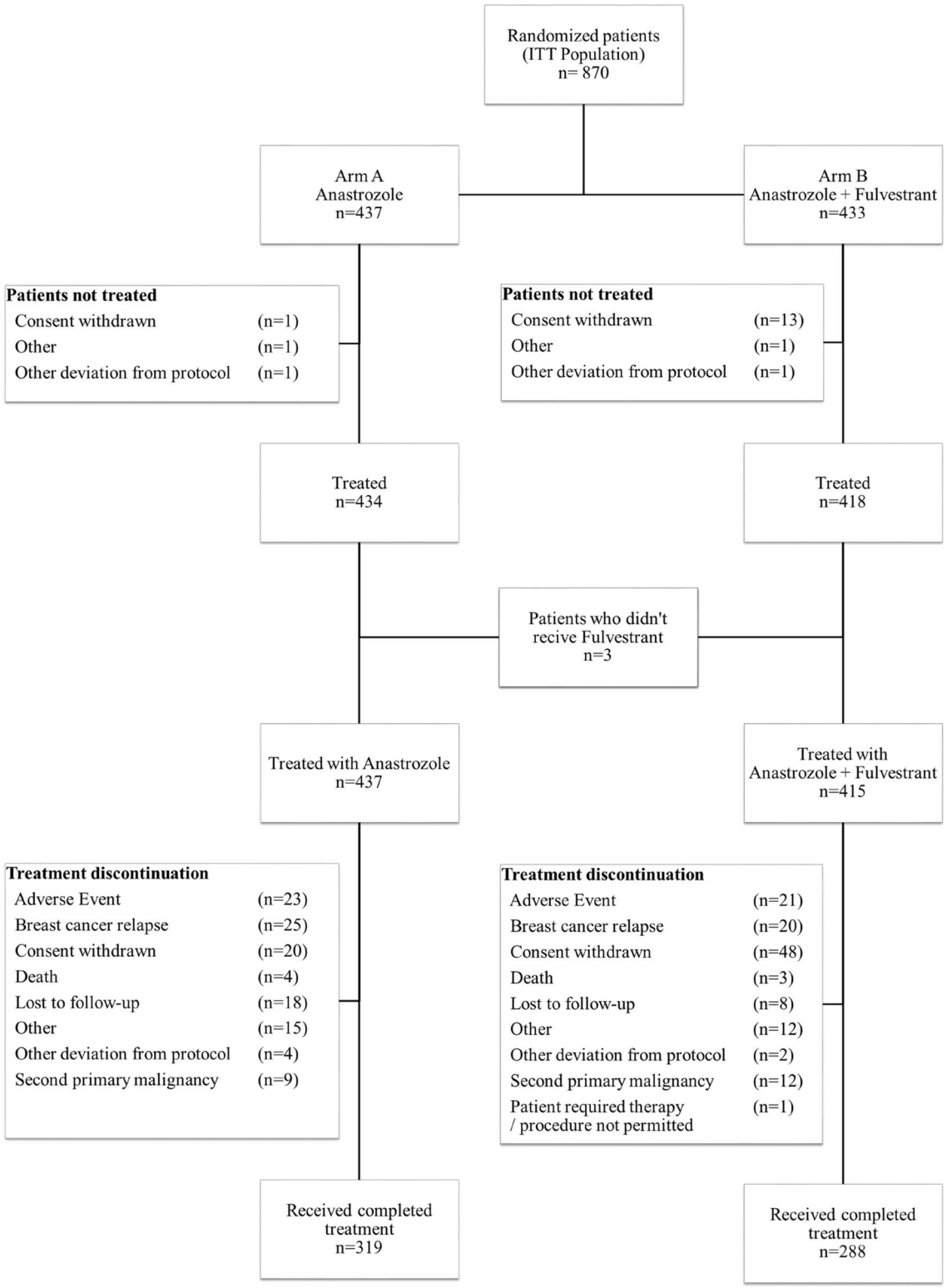



**Fig. 1** Consort study flowchart

**Table 1** Baseline patient and tumour characteristics and prior therapy

| | Anastrozole<br>*n* = 437 | Anastrozole + fulvestrant<br>*n* = 433 |
|---|---|---|
| Age at registration (years) | | |
| Median (range) | 62 (44–86) | 62 (40–85) |
| ECOG PS *n* (%) | | |
| 0 | 325 (74.4) | 330 (76.2) |
| 1 | 87 (19.9) | 85 (19.6) |
| 2 | 2 (0.5) | 1 (0.2) |
| Unknown | 23 (5.3) | 17 (3.9) |
| Breast surgery *n* (%) | | |
| Conservative | 310 (70.9) | 302 (69.7) |
| Mastectomy | 127 (29.1) | 131 (30.3) |
| Axillary surgery *n* (%) | | |
| Axillary lymph-node dissection | 281 (64.3) | 258 (59.6) |
| Sentinel lymph-node biopsy | 155 (35.5) | 174 (40.2) |
| Unknown | 1 (0.2) | 1 (0.2) |
| Tumour size *n* (%) | | |
| pT0 | 1 (0.2) | 0 (0.0) |
| pT1 | 242 (55.4) | 220 (50.8) |
| pT2 | 179 (41.0) | 189 (43.6) |
| pT3–T4 | 14 (3.2) | 22 (5.1) |
| Unknown | 1 (0.2) | 2 (0.5) |
| Nodal status *n* (%) | | |
| $pN0/N0_{(i+)}$ | 200 (45.8) | 214 (49.4) |
| pN1 | 164 (37.5) | 157 (36.3) |
| pN2 | 52 (11.9) | 42 (9.7) |
| pN3 | 18 (4.1) | 14 (3.2) |
| Unknown | 3 (0.7) | 6 (1.4) |
| Histological type *n* (%) | | |
| Invasive ductal carcinoma | 346 (79.2) | 337 (77.8) |
| Invasive lobular carcinoma | 71 (16.2) | 71 (16.4) |
| Other | 20 (4.6) | 25 (5.8) |
| Tumour grade *n* (%) | | |
| G1 | 82 (18.8) | 88 (20.3) |
| G2 | 235 (53.8) | 216 (49.9) |
| G3 | 83 (19.0) | 94 (21.7) |
| Unknown | 37 (8.5) | 35 (8.1) |
| Hormone receptor status *n* (%) | | |
| ER+ PgR+ | 385 (88.1) | 380 (87.8) |
| ER+ PgR− | 49 (11.2) | 52 (12.0) |
| ER− PgR+ | 3 (0.7) | 0 (0.0) |
| ER not assessable PgR+ | 0 (0.0) | 1 (0.2) |
| Prior chemotherapy setting *n* (%) | | |
| Adjuvant | 261 (59.7) | 256 (59.1) |
| Neoadjuvant | 34 (7.8) | 37 (8.5) |
| Neoadjuvant + adjuvant | 2 (0.5) | 3 (0.7) |
| None | 140 (32.0) | 137 (31.6) |
| Prior chemotherapy drugs (neo/adjuvant) *n* (%) | | |
| Anthracyclines + taxanes | 196 (44.9) | 193 (44.6) |
| Taxanes (other combinations) | 33 (7.6) | 29 (6.7) |
| Anthracyclines (other combinations) | 64 (14.6) | 71 (16.4) |
| CMF | 4 (0.9) | 1 (0.2) |
| Other combinations | 0 (0.0) | 2 (0.5) |

*ECOG PS* Eastern Cooperative Oncology Group performance status, *pT* pathological tumour size, *pN* pathological nodal status, *G* Grade, *ER* oestrogen receptor, *PgR* progesterone receptor, *C* cyclophosphamide, *M* methotrexate, *F* fluorouracil

**Table 2** Disease-free survival events

| | Anastrozole | Anastrozole + fulvestrant |
|---|---|---|
| | $n=437$ | $n=433$ |
| DFS event* *n* (%) | 62 (14.2) | 49 (11.3) |
| Type of event | | |
| Breast cancer relapse | 43 (9.8) | 35 (8.1) |
| Distant (± loco-regional) | 38 (8.7) | 31 (7.2) |
| Loco-regional only | 5 (1.1) | 4 (0.9) |
| Second primary breast cancer | 3 (0.7) | 1 (0.2) |
| Death without evidence of relapse | 16 (3.6) | 13 (3.0) |

*DFS* disease-free survival

*Statistically no significant: hazard ratio, 0.837; 95% CI 0.57 to 1.22; *p* 0.3511

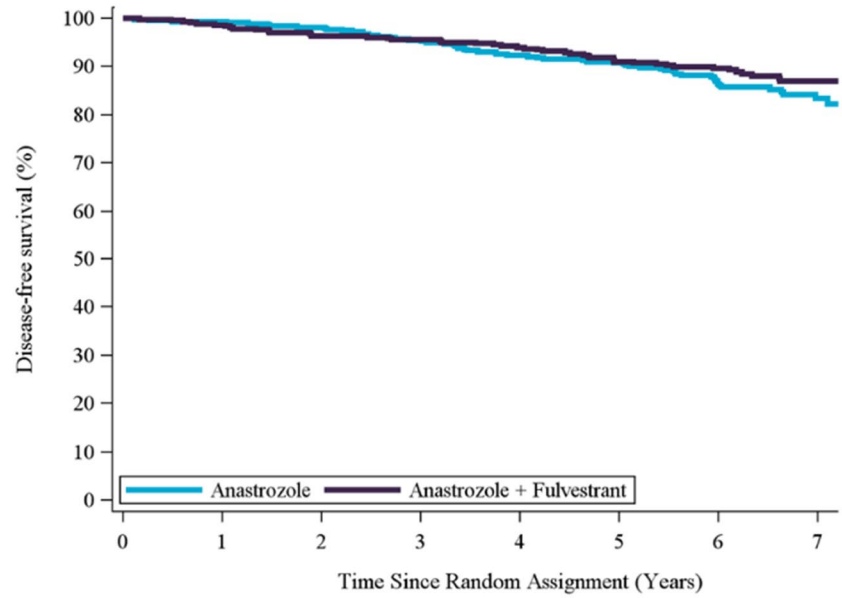
## Safety

Most relevant grade 2–3 related adverse events (> 5% in either arm, Table 3) with A versus A + F were joint pain (14.7% vs. 13.7%), fatigue (2.5% vs. 7.2%), bone pain (3% vs. 6.5%), hot flashes (3.5% vs. 5%) and muscle pain (2.8% vs. 5.1%). Five patients developed G4 toxicity, 3 in the A arm (GGT increase, pulmonary thromboembolism and cervix carcinoma) and 2 in the A + F arm (dilated cardiomyopathy and joint pain).

## Bone mineral density (BMD)

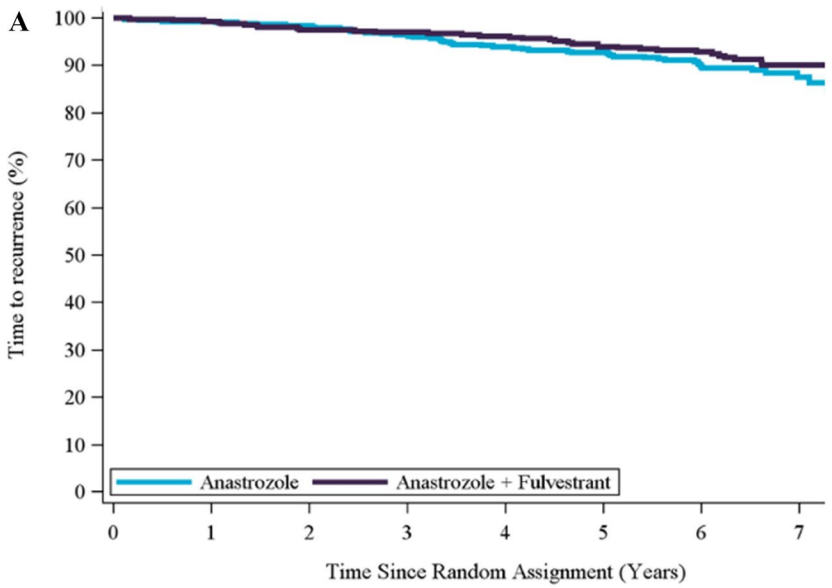
Baseline and follow-up DXA were available for 630 on hip and 553 patients on lumbar spine and were included in the analysis of the outcome of BMD. No differences were detected in BMD between baseline and follow-up DXA of hip ($p=0.811$) and lumbar spine ($p=0.478$), respectively. In addition, we performed a box plot graphic with the evolution of BMD measures with the repeated measures by treatment arm and no trend was detected (Fig. 4).

For the osteoporosis analysis, from the 639 patients with baseline and follow-up DXA in hip and/or lumbar spine, we excluded 105 patients that had osteopenia/osteoporosis at baseline. From these 534 patients, 21 (7.6%) and 13 (5.0%) were diagnosed of osteoporosis during follow-up in the A and A + F arms, respectively ($p=0.216$). Bone targeting agents were administered to 168 (31.5%) of the 534 patients analysed, 87 (31.6%) patients in arm A and 81 (31.3%) patients in arm A + F.




| Treatment | Total | Events n(%) | Censored n (%) | P long-rank | HR (95%CI) | P (Cox) | DFS 5 years |
|---|---|---|---|---|---|---|---|
| Anastrozole + Fulvestrant | 433 | 49 (11.3%) | 384 (88.7%) | 0.351 | Ref. | 0.352 | 91.0% |
| Anastrozole | 437 | 62 (14.2%) | 375 (85.8%) | | 0.84 (0.58, 1.22) | | 90.8% |

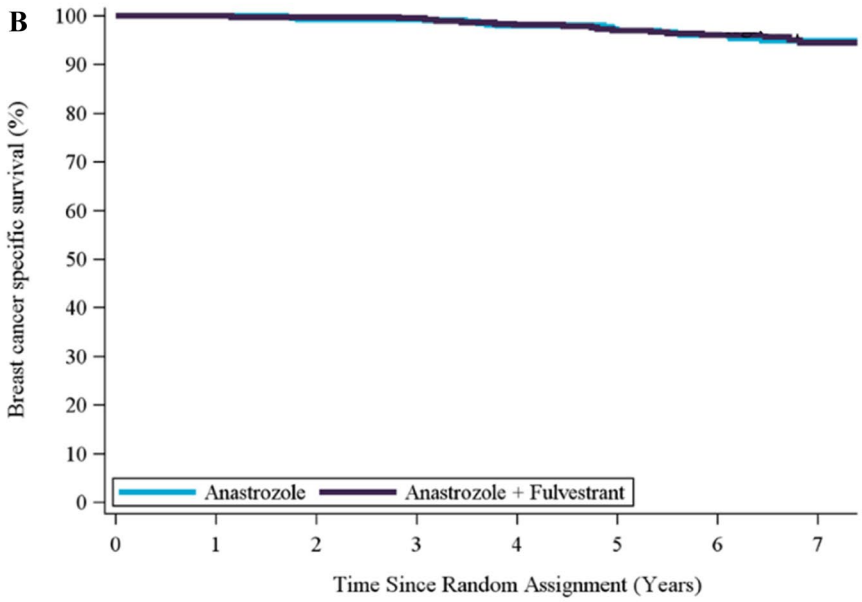
**Fig. 2** Disease-free survival




**At Risk, n**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| A+F | 433 | 405 | 377 | 364 | 353 | 339 | 277 | 93 |
| A | 437 | 425 | 410 | 390 | 372 | 361 | 276 | 99 |

| Treatment | Total | Events n(%) | Censored n (%) | P long-rank | HR (95%CI) | P (Cox) | DFS 5 years |
|---|---|---|---|---|---|---|---|
| Anastrozole + Fulvestrant | 433 | 36 (8.31%) | 397 (91.7%) | 0.406 | Ref. | 0.407 | 94.0% |
| Anastrozole | 437 | 46 (10.5%) | 391 (89.5%) | | 0.83 (0.54, 1.29) | | 92.6% |



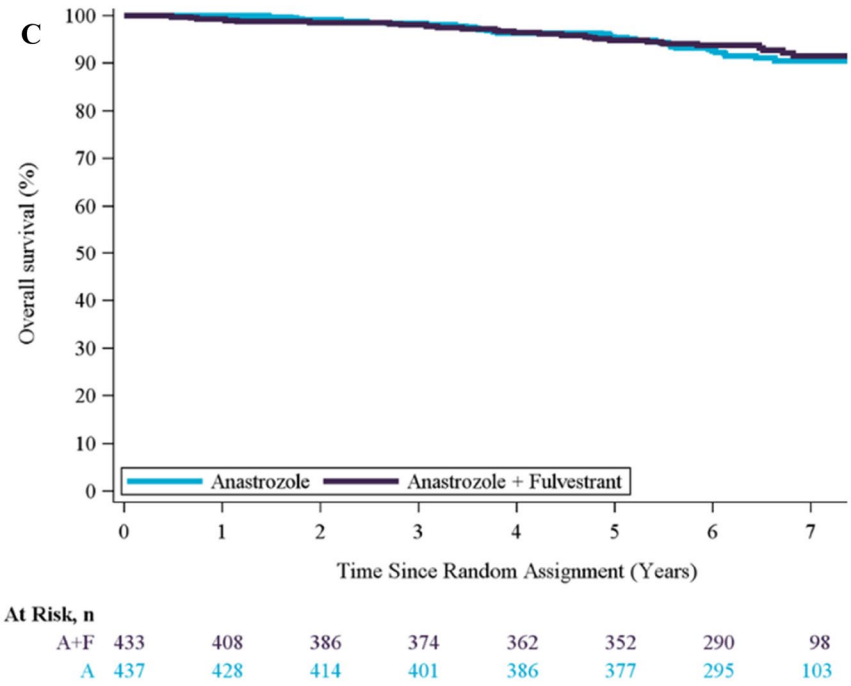

**At Risk, n**

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| A+F | 433 | 408 | 386 | 374 | 362 | 352 | 290 | 98 |
| A | 437 | 428 | 414 | 401 | 386 | 377 | 295 | 103 |

| Treatment | Total | Events n(%) | Censored n (%) | P long-rank | HR (95%CI) | P (Cox) | DFS 5 years |
|---|---|---|---|---|---|---|---|
| Anastrozole + Fulvestrant | 433 | 17 (3.93%) | 416 (96.1%) | 0.966 | Ref. | 0.966 | 97.1% |
| Anastrozole | 437 | 18 (4.12%) | 419 (95.9%) | | 0.99 (0.51, 1.91) | | 97.0% |

**Fig. 3** Other time to events: **a** time to recurrence, **b** breast cancer-specific survival and **c** overall survival

**Fig. 3** (continued)




| Treatment | Total | Events n(%) | Censored n (%) | P long-rank | HR (95%CI) | P (Cox) | DFS 5 years |
|---|---|---|---|---|---|---|---|
| Anastrozole + Fulvestrant | 433 | 28 (6.47%) | 405 (93.5%) | 0.558 | Ref. | 0.559 | 94.8% |
| Anastrozole | 437 | 34 (7.78%) | 403 (92.2%) | | 0.86 (0.52, 1.42) | | 95.3% |

**Table 3** Treatment related adverse events (NCI-CTCAE version 3.0)

| Adverse events (> 5% in either arm) *n* (%) | Anastrozole | | | Anastrozole + fulvestrant | | |
|---|---|---|---|---|---|---|
| | *n* = 437 | | | *n* = 415 | | |
| | Grade | | | Grade | | |
| | 2 | 3 | 4 | 2 | 3 | 4 |
| Bone pain | 13 (3.0) | – | – | 24 (5.8) | 3 (0.7) | – |
| Fatigue | 10 (2.3) | 1 (0.2) | – | 28 (6.7) | 2 (0.5) | – |
| Hot flushes | 13 (3.0) | 2 (0.5) | – | 18 (4.3) | 3 (0.7) | – |
| Joint pain | 54 (12.4) | 10 (2.3) | – | 46 (11.1) | 10 (2.4) | 1 (0.2) |
| Muscle pain | 10 (2.3) | 2 (0.5) | – | 19 (4.6) | 2 (0.5) | – |

*NCI-CTCAE* National Cancer Institute Common Terminology Criteria for Adverse Events

## Discussion

To the best of our knowledge, the GEICAM/2006–10 study is unique in testing fulvestrant in the adjuvant setting of breast cancer. The study addressed a relevant clinical question, i.e. the interest of adding fulvestrant to an AI, to test the hypothesis of whether a complete oestrogen blockade is superior to AIs alone in the adjuvant therapy of operable HR-positive/HER2-negative breast cancer. Anastrozole produces an intense decrease of serum estradiol levels, while fulvestrant downregulates the oestrogen receptor, preventing the appearance of resistance due to the stimulation of the receptor by trace amounts of estradiol and/or xenoestrogens [14, 15]. Unfortunately, the study was unable to provide a real conclusion due to the early stop of enrolment.

In the present analysis, the study results are formally negative, that is, adding fulvestrant to anastrozole did not improve DFS versus anastrozole alone. However, this conclusion should be taken with great caution due to a number of factors. First, the ability of the trial to rule out a clinically relevant benefit was scarce due to the small sample

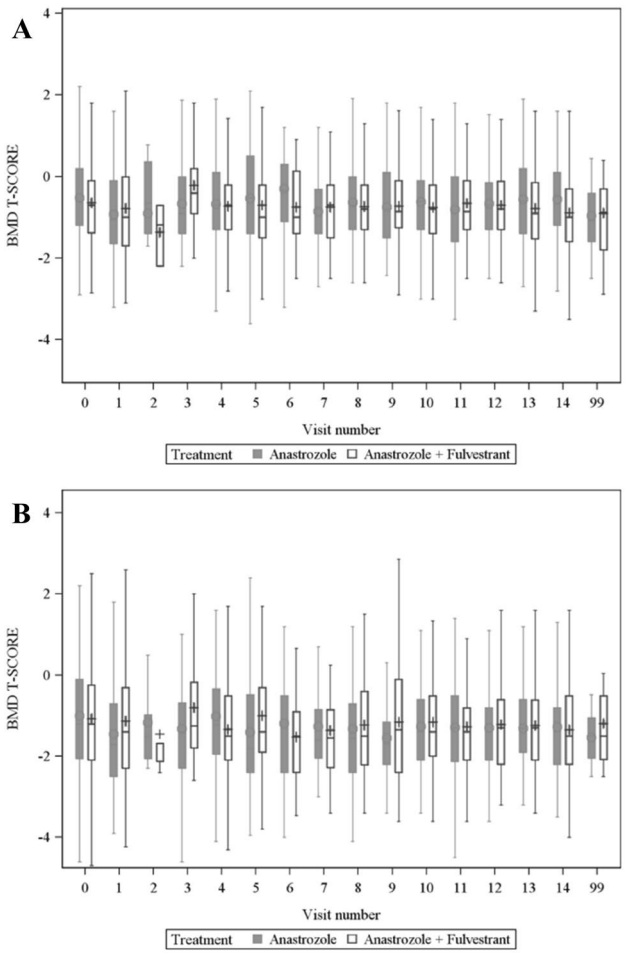



**Fig. 4** Box plot for BMD TSCORE: **a** Hip/Femur and **b** L1-L4

size achieved. Therefore, a false-negative result cannot be discarded. Second, the number of DFS events were numerically superior in the control arm than in the combination arm (62 vs. 49), resulting in a Hazard Ratio of 0.84 in favour of the experimental arm, though not statistically significant. Finally, the dose of fulvestrant used in the trial (250 mg IM every 4 weeks) could not be the most appropriate one, according to the results of the CONFIRM study in which a fulvestrant dose of 500 mg was associated with a statistically significant increase in PFS and OS compared with 250 mg [12, 13], added to this, adherence to fulvestrant treatment was suboptimal, this could have contributed to reduce the efficacy of the combination arm.

A very interesting observation in the GEICAM/2006–10 study is the sharp of the DFS curves, which seems to get apart from year 5 on. Late relapses, beyond 5 years and even later, are not rare in breast cancer patients with HR-positive tumours [16]. Therefore, further follow-up (already planned) could provide more information about the long-term effect of the experimental therapy in our population.

A final comment relevant to this trial that we are unable to omit is the weak situation of the independent research, the so-called Academia-sponsored research, in the current scenario of clinical research. The lack of funding resources independent from the pharmaceutical industry makes that studies of great clinical interest are never started or suffer early finalization, as it happened to the GEICAM/2006–10 trial. Although institutions such as EORTC, ESMO and others have attempted to find solutions [17], further efforts are necessary to solve this relevant problem.

## Conclusion

The GEICAM/2006–10 trial, comparing anastrozole to anastrozole plus fulvestrant as adjuvant therapy for HR-positive, HER2-negative operable breast cancer, did not find a statistically significant improvement with the combination of hormones. However, no firm conclusions can be drawn since the financer stopped the study after the entry of around a third of the planned population and there were numerically less DFS event in the anastrozole plus fulvestrant arm.

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## Compliance with ethical standards

**Conflict of interest** B Bermejo her institution has received research funding from AstraZeneca, Merck, Roche Pharma AG, Boehringer Ingelheim, Novartis and Roche outside the current trial. M. Ramos has participated in advisory boards of AstraZeneca, Roche, Novartis and Pfizer and received speaker honoraria from AstraZeneca, Roche, Novartis and Pfizer. J. Cruz has participated in advisory boards of AstraZeneca, Roche, Novartis, Pharmamar, Eisai, Lilly, Celgene, Astellas, Amgen, Glaxo, and Pfizer and received speaker honoraria from Glaxo, AstraZeneca, Roche, Novartis, Pharmamar, Eisai, Lilly, Celgene, Astellas, Amgen, and Pfizer. J.M. Baena-Cañada has participated in advisory boards of AstraZeneca, Roche, Novartis, Amgen, Bristol, Eisay, Celgene and Pfizer and received speaker honoraria from Roche and Ferrer. His institution has received research funding from AstraZeneca. B. Cirauqui has received speaker honoraria and funding for some independent medical education activities from Astra Zeneca outside de current trial. A Rodríguez-Lescure has participated in advisory boards of Roche, Novartis, MSD and Pfizer and has received speaker honoraria from AstraZeneca, Roche, Novartis, Kern Pharma, Amgen, and Pfizer; his institution has received research funding from Novartis, Pfizer, Lilly and Roche outside the current trial. E. Alba has

participated in advisory boards of Roche, Pfizer, Novartis and Lilly, his institution has received funding from Roche and Sysmex. N. Martínez Jañez has participated in advisory boards of AstraZeneca, Roche, Novartis, Celgene, Eisai, and Pfizer and received speaker honoraria from Roche, Novartis, Eisai and Pfizer. M. Muñoz: has participated in advisory boards of AstraZeneca, Merck and Novartis and expert opinion of Roche. She has received scientific meetings travel expenses from AstraZeneca and Roche. I. Álvarez López has participated in consultant or advisory boards of AstraZeneca, Pfizer, Palex, Roche, Novartis and received speaker honoraria from AstraZeneca, Pfizer, Roche, Eisai, received scientific meetings travel expenses from Pfizer and Roche. Her institution has received research funding from AstraZeneca, Pfizer, Roche, Novartis outside the current trial. A. Antón: has participated in consultant or advisory boards of Bayer. Him institution has received research funding from Roche outside the current trial. E. Carrasco´s immediate family member has participated in advisory boards of Pfizer and received speaker honoraria form Pfizer and his institution has received research funding from Pfizer. M. Martin has participated in advisory boards of AstraZeneca, Roche, Novartis, Pharmamar, Amgen, and Pfizer and received speaker honoraria from Glaxo, AstraZeneca, Roche, Novartis, Amgen, and Pfizer; his institution has received research funding from Novartis and Roche outside the current trial. E. Sevillano has received speaker honorary from Roche, Eisai, MSD and Ipsen. GEICAM has received funding from AstraZeneca for some independent medical education activities and research projects performed by the Group in which all authors collaborated. Rest of authors declare no conflict of interest.

**Ethical approval** The study was performed in accordance with the Declaration of Helsinki, approved by the institutions' ethical committees and health authorities in Spain, and registered at EUDRACT (2007-003417-14) and ClinicalTrials.gov (NCT00543127). Written informed consent was obtained from all patients before performing any protocol specific procedure.

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## Affiliations


**Manuel Ruíz-Borrego[1] · Angel Guerrero-Zotano[2] · Begoña Bermejo[3] · Manuel Ramos[4] · Josefina Cruz[5] · Jose Manuel Baena-Cañada[6] · Beatriz Cirauqui[7] · Álvaro Rodríguez-Lescure[8] · Emilio Alba[9] · Noelia Martínez-Jáñez[10] · Montserrat Muñoz[11] · Silvia Antolín[12] · Isabel Álvarez[13] · Sonia Del Barco[14] · Elena Sevillano[15] · José Ignacio Chacón[16] · Antonio Antón[17] · María José Escudero[18] · Victoria Ruiz[18] · Eva Carrasco[18] · Miguel Martín[19] on behalf of GEICAM**

[1] Department of Medical Oncology, H U Virgen del Rocio, Seville, Spain

[2] Department of Medical Oncology, Instituto Valenciano de Oncologia, Valencia, Spain

[3] Department of Medical Oncology, H Clinico de Valencia - Universidad de Valencia-CIBERONC, Valencia, Spain

[4] Department of Medical Oncology, Centro Oncologico de Galicia, A Coruña, Spain

[5] Department of Medical Oncology, H U de Canarias, Tenerife, Spain

[6] Department of Medical Oncology, H. U. Puerta del Mar, Instituto de Investigación e Innovación Biomédica de Cádiz (INiBICA), Cadiz, Spain

[7] Department of Medical Oncology, Badalona Applied Research Group in Oncology (B-ARGO Group), Catalan Institute of Oncology, Badalona, Spain

[8] Department of Medical Oncology, H G U de Elche, Alicante, Spain

[9] Department of Medical Oncology, Unidad de Oncología Médica Intercentros H. Regional y Universitario Virgen de la Victoria, IBIMA, Malaga, Spain

[10] Department of Medical Oncology, H U Ramon y Cajal, Madrid, Spain

[11] Department of Medical Oncology, H Clinic i Provincial de Barcelona, Translational Genomics and Targeted Therapeutics, Institut d´Investigacions Biomèdiques Pi I Sunyer-IDIBAPS, Barcelona, Spain

[12] Department of Medical Oncology, Complejo Hospitalario U A Coruña, A Coruña, Spain

[13] Department of Medical Oncology, H U Donostia, Donostia, Spain

[14] Department of Medical Oncology, Instituto Catalan de Oncologia de Girona, Hospital Universitario Josep Trueta, Girona, Spain

[15] Department of Medical Oncology, Centro Integral Oncologico Clara Campal, Madrid, Spain

[16] Department of Medical Oncology, H. Virgen de la Salud, Toledo, Spain

[17] Department of Medical Oncology, IIS Aragón, H U Miguel Servet, Saragossa, Spain

[18] GEICAM, Spanish Breast Cancer Group, Madrid, Spain

[19] Medical Oncology Department, Instituto de Investigación Sanitaria H. U. Gregorio Marañon, Universidad Complutense, CIBERONC, C/Dr. Esquerdo 46, 28009 Madrid, Spain