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Fulvestrant plus anastrozole or placebo versus exemestane alone after progression on non-steroidal aromatase inhibitors in postmenopausal patients with hormone-receptor-positive locally advanced or metastatic breast cancer (SoFEA): a composite, multicentre, phase 3 randomised trial

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Summary

Background The optimum endocrine treatment for postmenopausal women with advanced hormone-receptor-positive breast cancer that has progressed on non-steroidal aromatase inhibitors (NSAIs) is unclear. The aim of the SoFEA trial was to assess a maximum double endocrine targeting approach with the steroidal anti-oestrogen fulvestrant in combination with continued oestrogen deprivation.

Methods In a composite, multicentre, phase 3 randomised controlled trial done in the UK and South Korea, postmenopausal women with hormone-receptor-positive breast cancer (oestrogen receptor [ER] positive, progesterone receptor [PR] positive, or both) were eligible if they had relapsed or progressed with locally advanced or metastatic disease on an NSAI (given as adjuvant for at least 12 months or as first-line treatment for at least 6 months). Additionally, patients had to have adequate organ function and a WHO performance status of 0–2. Participants were randomly assigned (1:1:1) to receive fulvestrant (500 mg intramuscular injection on day 1, followed by 250 mg doses on days 15 and 29, and then every 28 days) plus daily oral anastrozole (1 mg); fulvestrant plus anastrozole-matched placebo; or daily oral exemestane (25 mg). Randomisation was done with computer-generated permuted blocks, and stratification was by centre and previous use of an NSAI as adjuvant treatment or for locally advanced or metastatic disease. Participants and investigators were aware of assignment to fulvestrant or exemestane, but not of assignment to anastrozole or placebo. The primary endpoint was progression-free survival (PFS). Analyses were by intention to treat. This trial is registered with ClinicalTrials.gov, numbers NCT00253422 (UK) and NCT00944918 (South Korea).

Findings Between March 26, 2004, and Aug 6, 2010, 723 patients underwent randomisation: 243 were assigned to receive fulvestrant plus anastrozole, 231 to fulvestrant plus placebo, and 249 to exemestane. Median PFS was 4·4 months (95% CI 3·4–5·4) in patients assigned to fulvestrant plus anastrozole, 4·8 months (3·6–5·5) in those assigned to fulvestrant plus placebo, and 3·4 months (3·0–4·6) in those assigned to exemestane. No difference was recorded between the patients assigned to fulvestrant plus anastrozole and fulvestrant plus placebo (hazard ratio 1·00, 95% CI 0·83–1·21; log-rank p=0·98), or between those assigned to fulvestrant plus placebo and exemestane (0·95, 0·79–1·14; log-rank p=0·56). 87 serious adverse events were reported: 36 in patients assigned to fulvestrant plus anastrozole, 22 in those assigned to fulvestrant plus placebo, and 29 in those assigned to exemestane. Grade 3–4 adverse events were rare; the most frequent were arthralgia (three in the group assigned to fulvestrant plus anastrozole; seven in that assigned to fulvestrant plus placebo; eight in that assigned to exemestane), lethargy (three; 11; 11), and nausea or vomiting (five; two; eight).

Interpretation After loss of response to NSAIs in postmenopausal women with hormone-receptor-positive advanced breast cancer, maximum double endocrine treatment with 250 mg fulvestrant combined with oestrogen deprivation is no better than either fulvestrant alone or exemestane.

Funding Cancer Research UK and AstraZeneca.

Introduction

The optimum endocrine treatment for postmenopausal women with advanced hormone-receptor-positive breast cancer that has progressed during treatment with non-steroidal aromatase inhibitors (NSAIs) is unclear.[1] The steroidal aromatase inactivator exemestane[2,3] and the steroidal oestrogen-receptor downregulator fulvestrant[4,5] have been recognised standards of care in this setting. The phase 3 EFECT trial[6] showed no difference in clinical efficacy between these two treatments for patients with oestrogen receptor (ER)-positive metastatic breast cancer in the first-line and second-line settings.

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*Listed in the appendix

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See Online for appendix

Treatment options in the setting of acquired resistance to NSAIs in ER-positive advanced breast cancer have changed since the results of the BOLERO-2 trial were reported.[7,8] This trial showed that progression-free survival (PFS) was longer with the combination of exemestane and the mTOR antagonist everolimus than with exemestane alone.[8] However, whether double endocrine targeting would be more effective than a partially non-cross-resistant endocrine agent in the setting of acquired resistance is unclear. Preclinical studies[9,10] have suggested that the efficacy of fulvestrant could be increased in a low oestrogen environment. As a competitive antagonist for ER, oestradiol can compete with fulvestrant for receptor-site occupancy. In MCF-7 aromatase-transfected xenografts, the combination of fulvestrant and an aromatase inhibitor was more effective than either treatment alone.[11,12] Furthermore, in model systems of acquired resistance to long-term oestrogen deprivation, breast cancer cells seem to be stimulated by low residual amounts of oestrogens, which potentially could be enhanced on withdrawal of oestrogen suppression at the time of progression.[13,14]

Thus, a maximum double endocrine targeting approach in the setting of acquired resistance to NSAIs should be investigated with fulvestrant in combination with continued oestrogen deprivation. The Study of Faslodex with or without concomitant Arimidex vs Exemestane following progression on non-steroidal Aromatase inhibitors (SoFEA) was designed. Exemestane was the appropriate standard of care (control) at the time the trial was designed and was compared with the then accepted optimum dosing schedule for fulvestrant.

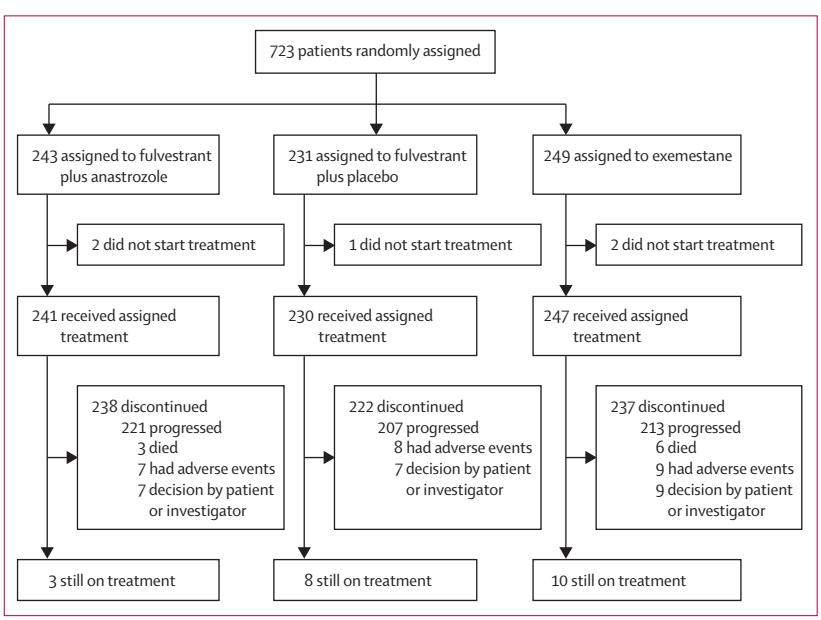

Figure 1: **Trial profile**

Methods

Study design and participants

SoFEA was a phase 3 multicentre randomised controlled trial that was done in 82 UK centres. Additionally, investigators in South Korea expressed interest in joining the trial. To simplify governance arrangements, a parallel trial, sponsored by AstraZeneca and following the SoFEA protocol and case report forms, was initiated. Patients were recruited from four South Korean centres. The SoFEA trial as presented here represents a composite of the UK and South Korean initiatives.

Postmenopausal women with hormone-receptor-positive breast cancer (ER positive or progesterone receptor [PR] positive, or both) were eligible if they relapsed or progressed with locally advanced or metastatic disease on an NSAI. The NSAI had to have been given as adjuvant treatment for at least 12 months, or as first-line treatment for locally advanced or metastatic disease for at least 6 months. Patients had to have adequate haematological, hepatic, and renal function, and a WHO performance status of 0–2. Patients already established on bisphosphonate treatment for at least 6 months or those who were due to start bisphosphonate treatment for bone metastases with other assessable sites of disease were eligible. Patients could have previously received tamoxifen and chemotherapy in the adjuvant or neoadjuvant setting or chemotherapy as first-line treatment for metastatic breast cancer followed by an NSAI alone for at least 6 months. Patients were excluded if they had rapidly progressing visceral disease, malignancies other than breast cancer in the previous 5 years (except for adequately treated in-situ carcinoma of the cervix, or basal-cell or squamous-cell carcinoma of the skin), or thrombocytopenia (because of the risk of bleeding with intramuscular injection of fulvestrant). Additionally, patients who had received systemic corticosteroids for more than 15 days in the 4 weeks before randomisation were excluded.

In the UK, this trial was approved by the Medicines and Healthcare products Regulatory Authority and South West 2 Multi-Research Ethics Committee (MREC 03/6/77). In South Korea, the study was approved by Korea Food and Drug Administration and local institutional review boards. All patients provided written informed consent. The Institute of Cancer Research-Clinical Trials and Statistics Unit (ICR-CTSU; London, UK) had overall responsibility for trial management; two additional collaborating trials units, Cancer Clinical Trials Team Information Services Division (Edinburgh, UK) and C+R Research (Seoul, South Korea), were responsible for regional data management. The trial management group was responsible for day-to-day running of the trial. The trial was overseen by an independent trial steering committee. Emerging safety and efficacy data were confidentially reviewed regularly by the independent data monitoring committee.

Randomisation and masking

Patients were randomly assigned (1:1:1) to receive fulvestrant plus anastrozole, fulvestrant plus placebo, or exemestane. Computer-generated permuted blocks were used, and stratification was by centre and previous use of an NSAI as adjuvant treatment or for locally advanced or metastatic disease. Independent randomisation was by telephone to ICR-CTSU and the Information Services Division in the UK and AstraZeneca in South Korea. Participants and investigators were aware of assignment to fulvestrant or exemestane, but not of assignment to anastrozole or placebo for patients in the groups assigned to fulvestrant.

Procedures

Fulvestrant was given with a loading dose schedule of a 500 mg intramuscular injection into the gluteus maximus on day 1, followed by 250 mg injections on days 15 and 29. Thereafter, 250 mg intramuscular injections were done every 28 days. Injections were given slowly, over the course of at least 2 min. Anastrozole (1 mg), matched placebo, and exemestane (25 mg) were given orally once daily. All treatments were given until disease progression or withdrawal.

Data for treatment compliance were obtained for fulvestrant only, for which a delay was allowed for recovery from toxic effects. Dose reductions are not standard for the treatments investigated in this trial. Timing of and reasons for treatment discontinuation were recorded. Fulvestrant, anastrozole, and the anastrozole-matched placebo were supplied by AstraZeneca. Exemestane was dispensed from hospital pharmacies or via the patient's primary-care physician.

Clinical assessment and toxicity reporting occurred monthly during the first 6 months, and every 3 months thereafter while treatment continued. Tumour assessment with Response Evaluation Criteria in Solid Tumors (RECIST; version 1.0) was done every 3 months and at discontinuation or withdrawal from treatment. Adverse events were graded according to National Cancer Institute Common Toxicity Criteria (version 3.0) and coded with the Medical Dictionary for Regulatory Activities (MedDRA; version 14.0), with central clinical review by SRDJ.

The primary endpoint was PFS, which was defined as time from randomisation to progression of existing disease, new sites of disease, second primary cancer if change in systemic treatment was necessary, or death from any cause. Secondary endpoints were overall survival (time from randomisation to death from any cause), objective response (proportion achieving complete or partial response on trial treatment), clinical benefit (proportion achieving complete or partial response, or stable disease for at least 6 months on trial treatment), duration of response or clinical benefit (PFS in patients who had an objective response or clinical benefit), time to treatment failure (not reported here), and tolerability and safety.

Plasma oestradiol concentrations at baseline and 3 months were also measured as an exploratory endpoint in a subset of patients who underwent randomisation after Nov 19, 2007, and who consented to and contributed at least one blood sample. Oestradiol analyses were done by Pharmanet (Princeton, NJ, USA) by gas chromatography tandem mass spectrometry with negative ion chemical ionisation after derivatisation of the steroid. The sensitivity of the assay was 0·625 pg/mL (2·3 pmol/L).

Statistical analysis

The sample size was based on two primary aims: to detect an improvement in median PFS from 5·5 to 7·5 months in patients allocated to fulvestrant plus anastrozole compared with fulvestrant plus placebo, and from 4·0 to 5·5 months in patients allocated to fulvestrant compared with exemestane. With a minimum follow-up of 6 months, 5% significance level (two-sided), and 90% power, 750 patients (250 per group) with 440 progression

	Fulvestrant plus anastrozole (n=243)	Fulvestrant plus placebo (n=231)	Exemestane (n=249)
Age at randomisation (years)	63·8 (57·0–72·0)	63·4 (57·0–73·5)	66·0 (59·2–75·0)
Hormone-receptor status			
ER positive, PR positive	120 (49%)	124 (54%)	132 (53%)
ER positive, PR negative	38 (16%)	33 (14%)	23 (9%)
ER positive, PR unknown	83 (34%)	71 (31%)	91 (37%)
ER negative or unknown, PR positive	2 (1%)	1 (<1%)	2 (1%)
ER unknown, PR unknown	0	2 (1%)	1 (<1%)
HER2 status			
Positive	17 (7%)	14 (6%)	17 (7%)
Negative	122 (50%)	141 (61%)	142 (57%)
Unknown	104 (43%)	76 (33%)	90 (36%)
Previous tamoxifen in adjuvant setting	171 (70%)	170 (74%)	166 (67%)
Time from primary diagnosis to first relapse (years)	5·0 (2·3–10·0)	5·1 (2·4–9·7)	5·2 (2·0–10·2)
Time on NSAI before randomisation (months)	21·5 (13·4–34·0)	21·2 (12·0–34·5)	20·1 (12·9–32·9)
Adjuvant	35·0 (24·0–44·7)	24·9 (17·4–41·9)	24·2 (18·5–41·9)
Locally advanced or metastatic breast cancer	20·1 (12·6–29·2)	18·6 (11·7–33·1)	19·3 (12·1–31·0)
NSAI setting and time on NSAI			
Adjuvant	42 (17%)	50 (22%)	42 (17%)
Locally advanced or metastatic breast cancer; <1 year	44 (18%)	49 (21%)	51 (20%)
Locally advanced or metastatic breast cancer; 1 to <2 years	87 (36%)	61 (26%)	88 (35%)
Locally advanced or metastatic breast cancer; ≥2 years	70 (29%)	71 (31%)	68 (27%)
Site of relapse*			
Visceral	138 (57%)	143 (62%)	145 (58%)
Soft tissue or node	68 (28%)	50 (22%)	71 (29%)
Bone	37 (15%)	37 (16%)	32 (13%)

Data are n (%) or median (IQR). ER=oestrogen receptor. PR=progesterone receptor. NSAI=non-steroidal aromatase inhibitor. *Data missing for one patient assigned to fulvestrant plus placebo and one assigned to exemestane.

Table 1: **Baseline characteristics**

events in the two fulvestrant groups were needed for the principal analysis. Because of a long period of recruitment, in 2010, the independent data monitoring committee agreed that the data were sufficiently mature for 723 enrolled patients to answer the principal questions with the same number of events, but in a smaller total number of patients who had been followed up for a longer period than originally anticipated.

The principal efficacy analyses included all patients who underwent randomisation on an intention-to-treat basis. Survival endpoints were shown graphically with Kaplan-Meier plots, and treatment comparisons made with the log-rank test. Hazard ratios (HRs) were obtained from Cox proportional hazards regression models, with HRs of less than 1 favouring fulvestrant plus anastrozole in the comparison of fulvestrant plus placebo and fulvestrant plus anastrozole, and fulvestrant plus placebo in the comparison of fulvestrant plus placebo and exemestane. The proportionality assumption of the Cox model was tested with Schoenfeld residuals, and was shown to hold.

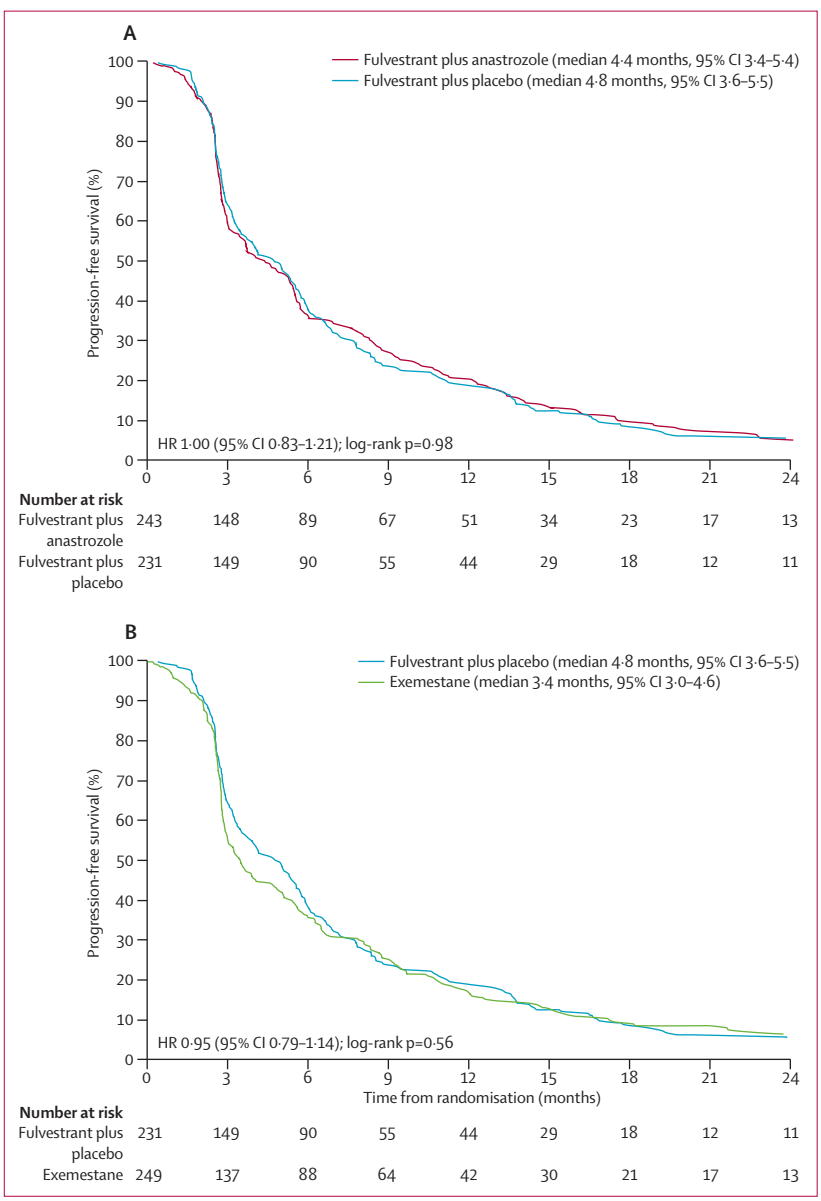

Figure 2: **Progression-free survival**
(A) Fulvestrant plus anastrozole *vs* fulvestrant plus placebo. (B) Fulvestrant plus placebo *vs* exemestane. HR=hazard ratio.

Subgroup analyses were reported with forest plots for age at randomisation, ER and PR status, HER2 status, time from diagnosis to first relapse, dominant site of relapse, and NSAI setting and time on NSAI combined. In view of the absence of standard prognostic factors in this setting, and to avoid overparameterisation of a multivariable model, baseline characteristics were assessed for prognostic ability, irrespective of treatment effect. Variables shown to be significant were combined in a multivariable model with a forward stepwise method. Treatment was then added to the model to obtain the adjusted HR for treatment effect. Proportions of responses were compared with Fisher's exact tests.

Safety analyses were done for all patients who received at least one dose of trial treatment (as treated population). The worst grade of adverse event during trial treatment was reported and compared with Fisher's exact tests. All prespecified toxic effects and any MedDRA-coded event satisfying predefined criteria (ie, ≥10% frequency, p<0·01, or >1% difference in frequency between treatment groups) are presented. A significance level of <0·01 allowed some adjustment for multiple testing of toxicity endpoints. Geometric mean oestradiol concentrations were calculated by treatment group at each timepoint.

This analysis includes all data received and processed by Jan 3, 2012. Data were collated at ICR-CTSU, where all interim and final analyses were done. Central statistical monitoring was done by ICR-CTSU and was supplemented by selected on-site source document verification. All analyses were done in Stata (version 10.1).

This trial is registered as an International Standard Randomised Controlled Trial, number ISRCTN44195747, and with ClinicalTrials.gov, numbers NCT00253422 (UK) and NCT00944918 (South Korea).

Role of the funding source

The trial was cosponsored by The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research in the UK; AstraZeneca sponsored the trial in South Korea. The funders had no role in data collection, data analysis, data interpretation, or writing of the report. The study design was peer-reviewed by Cancer Research UK and the protocol was approved by the trial sponsors and AstraZeneca. SRDJ, LSK, and JMB had full access to all the data in the study, and SRDJ had final responsibility for the decision to submit for publication.

Results

Between March 26, 2004, and Aug 6, 2010, 723 patients underwent randomisation (figure 1): 698 from the UK

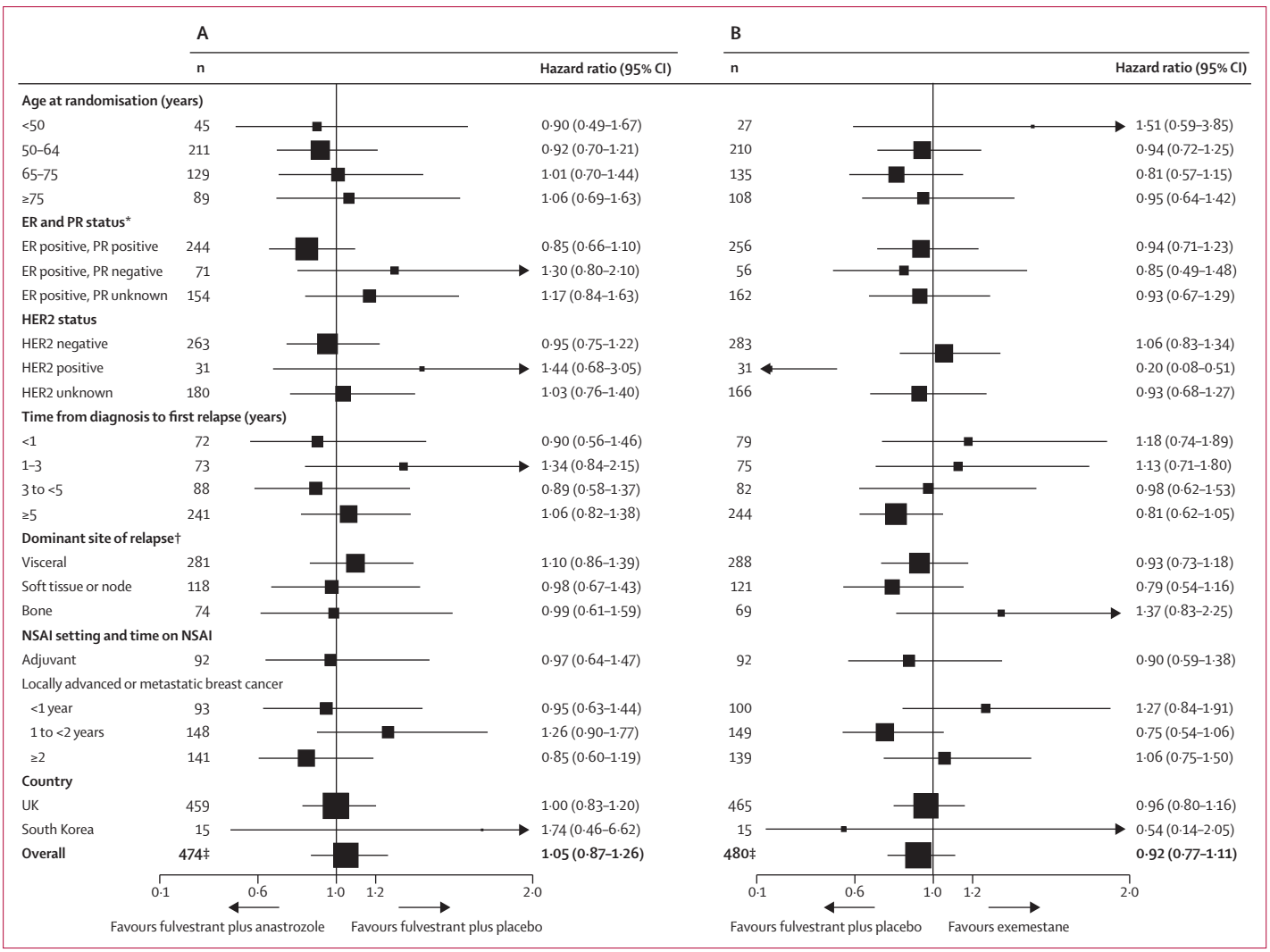

Figure 3: **Subgroup analyses of progression-free survival**

(A) Fulvestrant plus anastrozole *vs* fulvestrant plus placebo. (B) Fulvestrant plus placebo *vs* exemestane. ER=oestrogen receptor. PR=progesterone receptor. NSAI=non-steroidal aromatase inhibitor. *Data for the few patients with ER-negative or unknown, and PR-positive disease, and those with unknown hormone-receptor-status not shown here. †Data missing for one patient assigned to fulvestrant plus placebo and one assigned to exemestane. ‡Adjusted for time from diagnosis to first relapse, number of disease sites at baseline, and NSAI setting and time on NSAI.

and 25 from South Korea. Baseline characteristics, such as time from diagnosis to first relapse and sites of dominant disease, are representative of a population of patients with hormone-receptor-positive metastatic breast cancer (table 1). 589 (81%) had previously received an NSAI in the locally advanced or metastatic setting for a median of 19·3 months (IQR 12·1–31·2; table 1), suggesting that this population had a good response to previous NSAI treatment. Four patients assigned to fulvestrant plus anastrozole missed a fulvestrant injection, and 109 patients (50 assigned to fulvestrant plus anastrozole; 59 assigned to fulvestrant plus placebo) had at least one scheduled fulvestrant dose delay.

After a median follow-up in all patients of 37·9 months (IQR 23·1–50·8), 689 progression events were reported: 235 in patients assigned to fulvestrant plus anastrozole, 221 in those assigned to fulvestrant plus placebo, and 233 in those assigned to exemestane. No difference in PFS was recorded between patients assigned to fulvestrant plus anastrozole and fulvestrant plus placebo, or between those assigned to fulvestrant plus placebo and exemestane (figure 2). A multivariable analysis with adjustment for time from diagnosis to first relapse, number of disease sites present at baseline, and NSAI setting and time on NSAI did not substantially affect estimates of treatment effect (fulvestrant plus anastrozole *vs* fulvestrant plus placebo: HR 1·05, 95% CI 0·87–1·26, p=0·62; fulvestrant plus placebo *vs* exemestane: 0·92, 0·77–1·11, p=0·41). Subgroup analyses were consistent with the overall effect on PFS (figure 3).

508 patients had died: 168 (69%) assigned to fulvestrant plus anastrozole, 167 (72%) to fulvestrant plus placebo,

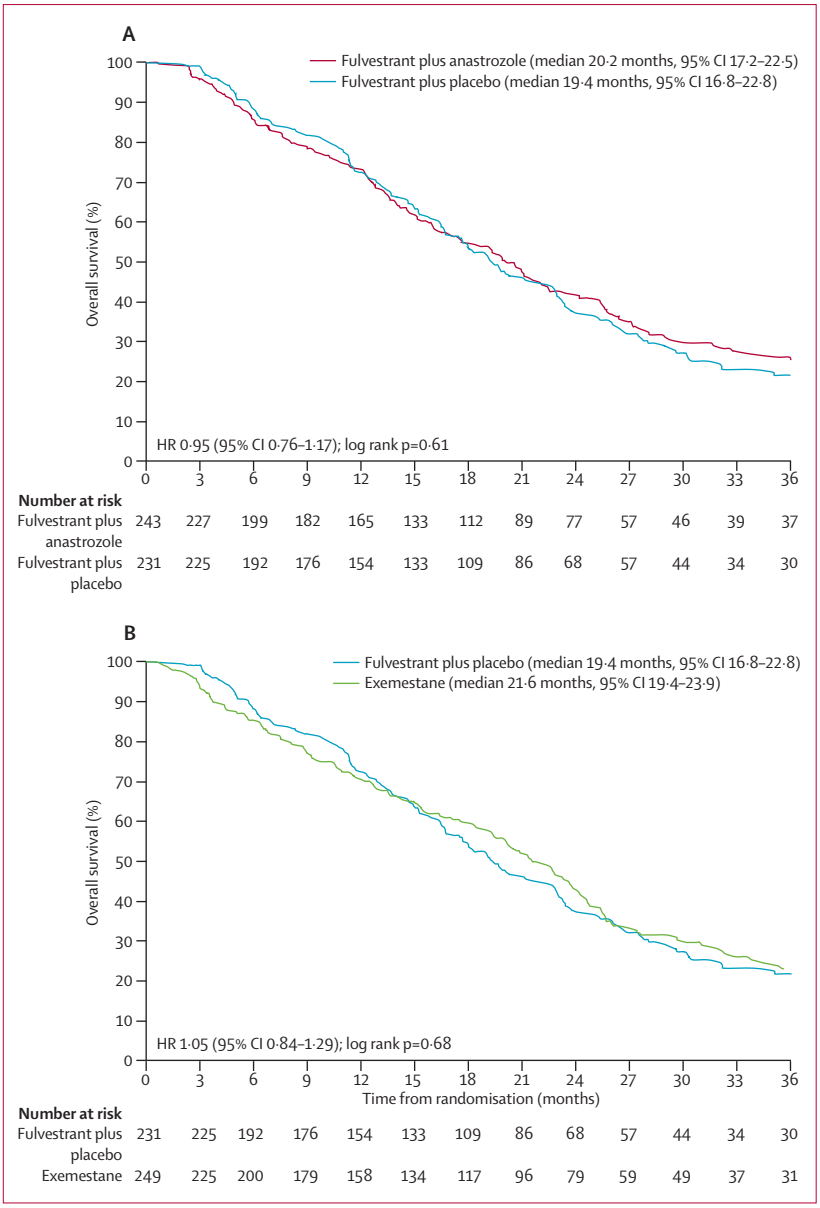

Figure 4: **Overall survival**
(A) Fulvestrant plus anastrozole *vs* fulvestrant plus placebo. (B) Fulvestrant plus placebo *vs* exemestane. HR=hazard ratio.

and 173 (69%) to exemestane. Most deaths were due to breast cancer. Only 12 deaths were reportedly due to other causes: cardiovascular (one patient assigned to fulvestrant plus anastrozole, two to fulvestrant plus placebo), cerebrovascular (one assigned to fulvestrant plus placebo, one to exemestane), primary lung cancer (one assigned to fulvestrant plus placebo, one to exemestane), pneumonia (one assigned to fulvestrant plus anastrozole, one to exemestane), neutropenic sepsis (one assigned to fulvestrant plus placebo), and unknown (one assigned to fulvestrant plus anastrozole, one to exemestane). Only two of the deaths due to causes other than breast cancer (one pneumonia and one unknown) occurred on trial treatment, and neither was deemed to be related to treatment.

No difference in overall survival was recorded between patients assigned to fulvestrant plus anastrozole and fulvestrant plus placebo, or between those assigned to fulvestrant plus placebo and exemestane (figure 4). Subgroup analyses were consistent with the overall effect on overall survival (appendix).

In the intention-to-treat population, 18 (7%) of 243 patients assigned to fulvestrant plus anastrozole had objective tumour responses (one complete response, 17 partial response), as did 16 (7%) of 231 assigned to fulvestrant plus placebo (all partial response), and nine (4%) of 249 assigned to exemestane (two complete response, seven partial response; fulvestrant plus anastrozole *vs* fulvestrant plus placebo: p=0·88; fulvestrant plus placebo *vs* exemestane: p=0·27). 558 patients (77%) had measurable disease: 194 (80%) assigned to fulvestrant plus anastrozole, 178 (77%) to fulvestrant plus placebo, and 186 (75%) to exemestane. Of these patients, 15 (8%) patients assigned to fulvestrant plus anastrozole achieved objective responses (all partial response), as did 14 (8%) assigned to fulvestrant plus placebo (all partial response), and seven (4%) assigned to exemestane (one complete response, six partial response; fulvestrant plus anastrozole *vs* fulvestrant plus placebo: p=1·00; fulvestrant plus placebo *vs* exemestane: p=0·17). Median duration of objective response was 12·3 months (IQR 5·7–22·1) for patients assigned to fulvestrant plus anastrozole, 16·5 months (7·8–29·2) for those assigned to fulvestrant plus placebo, and 17·2 months (9·6–26·9) for those assigned to exemestane.

82 patients (34%) assigned to fulvestrant plus anastrozole, 73 (32%) assigned to fulvestrant plus placebo, and 67 (27%) assigned to exemestane achieved clinical benefit (fulvestrant plus anastrozole *vs* fulvestrant plus placebo: p=0·75; fulvestrant plus placebo *vs* exemestane: p=0·27). In patients with measurable disease, 63 (33%) assigned to fulvestrant plus anastrozole, 55 (31%) assigned to fulvestrant plus placebo, and 43 (23%) assigned to exemestane achieved clinical benefit (fulvestrant plus anastrozole *vs* fulvestrant plus placebo: p=0·94; fulvestrant plus placebo *vs* exemestane: p=0·16). Median duration of clinical benefit was 13·0 months (8·9–18·9) for patients assigned to fulvestrant plus anastrozole, 13·0 months (8·3–17·5) for those assigned to fulvestrant plus placebo, and 13·0 months (9·3–21·7) for those assigned to exemestane.

87 serious adverse events were reported, of which three were suspected unexpected serious adverse reactions (one in the group assigned to fulvestrant plus anastrozole and two in the group assigned to fulvestrant plus placebo) and 11 were serious adverse reactions (six in the group assigned to fulvestrant plus anastrozole, three in that assigned to fulvestrant plus placebo, and

	Fulvestrant plus anastrozole (n=241)		Fulvestrant plus placebo (n=230)		Exemestane (n=247)		p value fulvestrant plus anastrozole *vs* fulvestrant plus placebo	p value fulvestrant plus placebo *vs* exemestane
	Any grade	Grades 3 and 4	Any grade	Grades 3 and 4	Any grade	Grades 3 and 4		
Upper abdominal pain	3 (1%)	0	1 (<1%)	0	5 (2%)	1 (<1%)	0·62	0·22
Alopecia*	25 (10%)	0	31 (13%)	0	32 (13%)	0	0·32	0·89
Anaemia	5 (2%)	0	3 (1%)	1 (<1%)	6 (2%)	2 (1%)	0·73	0·51
Arthralgia*	97 (40%)	3 (1%)	98 (43%)	7 (3%)	115 (47%)	8 (3%)	0·64	0·41
Back pain	18 (7%)	1 (<1%)	23 (10%)	0	18 (7%)	1 (<1%)	0·41	0·33
Bone pain	21 (9%)	3 (1%)	13 (6%)	3 (1%)	17 (7%)	3 (1%)	0·22	0·71
Breast pain	5 (2%)	1 (<1%)	3 (1%)	0	7 (3%)	0	0·73	0·34
Cellulitis	4 (2%)	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0·37	1·00
Chest pain	6 (2%)	1 (<1%)	8 (3%)	4 (2%)	11 (4%)	0	0·60	0·65
Constipation*	64 (27%)	2 (1%)	57 (25%)	0	58 (23%)	1 (<1%)	0·67	0·75
Cough	8 (3%)	0	20 (9%)	1 (<1%)	17 (7%)	0	0·02	0·50
Decreased appetite*	73 (30%)	1 (<1%)	63 (27%)	3 (1%)	70 (28%)	3 (1%)	0·54	0·84
Diarrhoea*	40 (17%)	1 (<1%)	53 (23%)	2 (1%)	47 (19%)	0	0·08	0·31
Dizziness	12 (5%)	0	9 (4%)	0	16 (6%)	0	0·66	0·23
Dry skin	0	0	6 (3%)	0	3 (1%)	0	0·01	0·32
Dysgeusia	2 (1%)	0	4 (2%)	0	1 (<1%)	0	0·44	0·20
Dyspepsia*	52 (22%)	0	59 (26%)	1 (<1%)	72 (29%)	0	0·33	0·41
Dysphagia	0	0	3 (1%)	0	1 (<1%)	0	0·12	0·36
Dysphonia	0	0	3 (1%)	0	2 (1%)	0	0·12	0·68
Dyspnoea	17 (7%)	1 (<1%)	35 (15%)	5 (2%)	26 (11%)	2 (1%)	0·005	0·13
Fatigue	7 (3%)	1 (<1%)	8 (3%)	2 (1%)	11 (4%)	0	0·80	0·65
Headache*	49 (20%)	1 (<1%)	64 (28%)	2 (1%)	52 (21%)	1 (<1%)	0·07	0·09
Hot flush*	88 (37%)	2 (1%)	81 (35%)	5 (2%)	83 (34%)	1 (<1%)	0·77	0·77
Hyperhidrosis	4 (2%)	0	1 (<1%)	0	1 (<1%)	0	0·37	1·00
Hypertension	4 (2%)	2 (1%)	3 (1%)	1 (<1%)	0	0	1·00	0·11
Hypotension	0	0	3 (1%)	0	1 (<1%)	1 (<1%)	0·12	0·36
Infection	1 (<1%)	0	1 (<1%)	0	8 (3%)	0	1·00	0·04
Insomnia*	75 (31%)	1 (<1%)	63 (27%)	5 (2%)	72 (29%)	3 (1%)	0·42	0·69
Joint swelling	3 (1%)	0	4 (2%)	0	1 (<1%)	0	0·72	0·20
Lethargy*	151 (63%)	3 (1%)	144 (63%)	11 (5%)	134 (54%)	11 (5%)	1·00	0·08
Localised infection	1 (<1%)	0	1 (<1%)	0	4 (2%)	0	1·00	0·37
Lower-respiratory-tract infection	17 (7%)	2 (1%)	15 (7%)	0	13 (5%)	2 (1%)	0·86	0·57
Lymphoedema	6 (2%)	0	2 (1%)	0	4 (2%)	0	0·29	0·69
Altered mood*	53 (22%)	0	56 (24%)	3 (1%)	60 (24%)	1 (<1%)	0·59	1·00
Mucosal inflammation*	15 (6%)	0	22 (10%)	0	15 (6%)	0	0·23	0·17
Muscular weakness	3 (1%)	0	0	0	2 (1%)	0	0·25	0·50
Musculoskeletal chest pain	8 (3%)	0	7 (3%)	0	5 (2%)	1 (<1%)	1·00	0·57
Musculoskeletal pain	11 (5%)	0	6 (3%)	1 (<1%)	6 (2%)	1 (<1%)	0·33	1·00
Myalgia	10 (4%)	0	5 (2%)	1 (<1%)	5 (2%)	0	0·30	1·00
Nausea or vomiting*	83 (34%)	5 (2%)	100 (43%)	2 (1%)	92 (37%)	8 (3%)	0·05	0·19
Neck pain	2 (1%)	2 (1%)	1 (<1%)	0	4 (2%)	0	1·00	0·37
Peripheral neuropathy	1 (<1%)	0	6 (3%)	1 (<1%)	5 (2%)	0	0·06	0·77
Peripheral oedema	8 (3%)	0	3 (1%)	0	6 (2%)	0	0·22	0·51
Oral candidosis	0	0	3 (1%)	0	0	0	0·12	0·11
Oropharyngeal pain	3 (1%)	0	4 (2%)	0	0	0	0·72	0·05
Pain	4 (2%)	0	15 (7%)	3 (1%)	10 (4%)	2 (1%)	0·009	0·30
Pain in extremity	15 (6%)	0	6 (3%)	0	13 (5%)	0	0·07	0·16
Paraesthesia	4 (2%)	0	1 (<1%)	0	3 (1%)	0	0·37	0·62
Pruritus	4 (2%)	0	3 (1%)	0	6 (2%)	0	1·00	0·51

(Continues on next page)

	Fulvestrant plus anastrozole (n=241)		Fulvestrant plus placebo (n=230)		Exemestane (n=247)		p value fulvestrant plus anastrozole *vs* fulvestrant plus placebo	p value fulvestrant plus placebo *vs* exemestane
	Any grade	Grades 3 and 4	Any grade	Grades 3 and 4	Any grade	Grades 3 and 4		
(Continued from previous page)								
Rash	6 (2%)	0	4 (2%)	0	9 (4%)	0	0·75	0·26
Sciatica	4 (2%)	1 (<1%)	2 (1%)	0	1 (<1%)	0	0·69	0·61
Sinusitis	0	0	0	0	3 (1%)	0	..	0·25
Swelling	1 (<1%)	0	1 (<1%)	0	4 (2%)	0	1·00	0·37
Tooth infection	0	0	3 (1%)	0	0	0	0·12	0·11
Urinary-tract infection	7 (3%)	0	14 (6%)	0	8 (3%)	2 (1%)	0·12	0·19
Vaginal haemorrhage	4 (2%)	0	2 (1%)	0	0	0	0·69	0·23
Blurred vision	0	0	1 (<1%)	0	3 (1%)	1 (<1%)	0·49	0·62
Vulvovaginal dryness	2 (1%)	0	7 (3%)	0	2 (1%)	0	0·10	0·10
Weight loss	2 (1%)	0	3 (1%)	0	5 (2%)	1 (<1%)	0·68	0·73

Adverse events measured with Common Toxicity Criteria (version 3.0). *Prespecified.

Table 2: **Adverse events**

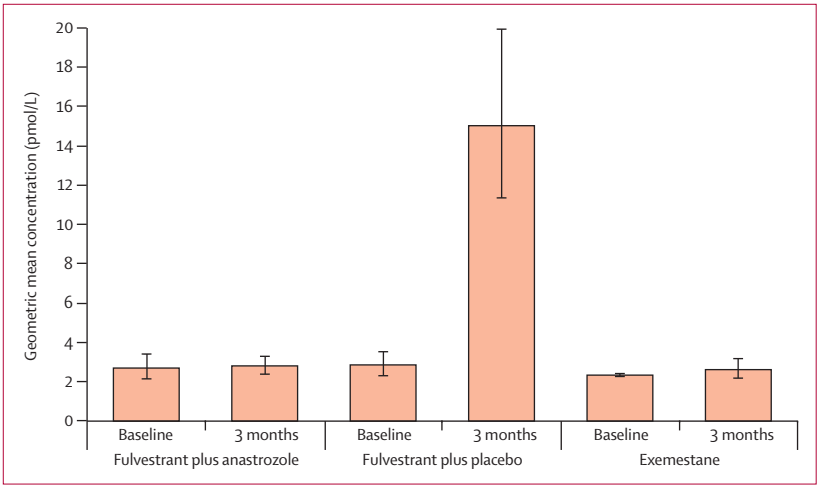

Figure 5: **Oestradiol concentration**
Error bars show 95% CI.

two in that assigned to exemestane). Of the other 73 serious adverse events, 29 were in the group assigned to fulvestrant plus anastrozole, 17 in that assigned to fulvestrant plus placebo, and 27 in that assigned to exemestane. Frequency of dyspnoea and pain (any grade) was higher in patients assigned to fulvestrant plus placebo than in those assigned to fulvestrant plus anastrozole; no other differences between groups were noted (table 2). Grade 3 and 4 adverse events were rare; the most frequent were arthralgia, lethargy, and nausea or vomiting (table 2).

Oestradiol concentrations in 94 (26%) of 363 patients who underwent randomisation after Nov 19, 2007, showed that oestrogen continued to be suppressed at 3 months in patients assigned to fulvestrant plus anastrozole and exemestane, but not in those assigned to fulvestrant plus placebo (figure 5).

Discussion

Our study shows no benefit for the combination of fulvestrant and anastrozole in the setting of acquired endocrine resistance in hormone-receptor-positive breast cancer compared with fulvestrant alone. Likewise, no significant difference was reported between fulvestrant alone and exemestane, confirming the results of EFECT[6] (panel). These results provide clear evidence that endocrine treatment after loss of response to NSAIs in hormone-receptor-positive advanced breast cancer has little efficacy, with a median PFS of only about 3–4 months. So, does combined maximum endocrine treatment have any role as a treatment option for hormone-receptor-positive advanced breast cancer?

SoFEA differed from two other trials of fulvestrant (250 mg) plus anastrozole in the first-line setting,[15,16] in terms of the comparator and the patients studied (second-line with acquired endocrine resistance). In the FACT study,[15] no difference was reported for time to disease progression between fulvestrant plus anastrozole and anastrozole alone. However, in the SWOG 0226 study,[16] a significant difference between these regimens was reported in both PFS and overall survival, although the benefit seemed to be restricted to the 60% of study patients who had received no previous adjuvant endocrine treatment. Thus, although fulvestrant combined with an aromatase inhibitor might be no better than either fulvestrant or exemestane alone in the second-line endocrine resistant setting, dual endocrine targeting could still be beneficial in the true first-line hormone-sensitive setting. In preclinical models of hormone-sensitive breast cancer,[11,12] the combination of fulvestrant plus anastrozole produced the greatest tumour inhibition compared with either drug alone. Notably in our study, patients with known ER-positive and PR-positive tumours seemed to show the greatest benefit for fulvestrant plus anastrozole,

Panel: Research in context

Systematic review

A comprehensive search for all available data and continuing trials reported in English was done in November, 2002. The search confirmed that no randomised trials of fulvestrant after treatment with non-steroidal aromatase inhibitors (NSAIs) in advanced breast cancer had been reported at the time this study was developed; therefore, no formal systematic review could be done. The best possible endocrine treatment in the group of patients identified for SoFEA was unclear, and evidence suggested that, despite acquired endocrine resistance, patients might derive clinical benefit from further endocrine treatment.[1] Furthermore, preclinical studies[9–12] suggested that fulvestrant could have improved efficacy in a low-oestrogen environment, providing a clear rationale for exploration of maximum endocrine treatment in the setting of resistance to NSAI.

Interpretation

Investigation of fulvestrant in the setting of acquired resistance to NSAIs is unique to SoFEA, which thus supplements the results of the EFECT trial of fulvestrant versus exemestane.[6] SoFEA has provided evidence that after progression on NSAI, endocrine treatment options, such as exemestane or fulvestrant (with or without continued oestrogen suppression), give a median progression-free survival of only 3–4 months. However, the role of maximum dual endocrine treatment combining fulvestrant at the now approved increased dosing schedule and an aromatase inhibitor remains to be examined in true first-line endocrine-sensitive advanced breast cancer.

potentially indicating a group of patients with endocrine-responsive disease. However, despite recruitment of only patients with acquired resistance, heterogeneity in large phase 3 studies inevitably yields a mixed population of patients with ER-positive advanced breast cancer in terms of true endocrine responsiveness, which makes identification of those who could derive benefit from combined maximum endocrine treatment challenging.

The effect of fulvestrant (with or without concomitant oestrogen suppression) might not have been better than that of exemestane in our trial because of a suboptimum dose of fulvestrant. Fulvestrant has a dose–response effect on both ER downregulation and cell proliferation (as assessed by the proliferation marker Ki-67).[17] Since SoFEA was initiated, two studies have suggested that fulvestrant's efficacy is increased at the monthly 500 mg intramuscular dose: the phase 2 FIRST study[18] and subsequently in the larger phase 3 randomised CONFIRM study.[19] The monthly 500 mg intramuscular dose of fulvestrant, with a loading dose schedule, was approved in 2010.

The blood samples we analysed provide evidence to suggest that relapse on NSAIs is not associated with loss of oestrogen suppression. Instead, intracellular signalling mechanisms for acquired resistance to these treatments probably exist because of either growth factor crosstalk or activation of other key regulatory and survival pathways.[7] Targeting of signalling pathways at time of endocrine resistance has been shown to be effective by the size of PFS improvement in BOLERO-2 in this setting:[8] median PFS was 10·6 months in patients assigned to exemestane and everolimus and 4·1 months in those assigned to exemestane alone (HR 0·36, 95% CI 0·27–0·47; p<0·001). Notably, the populations studied in SoFEA and BOLERO-2 were similar in terms of age, previous use of adjuvant endocrine treatment, and, importantly, previous endocrine sensitivity. Additionally, efficacy results for the control group who received exemestane were similar in the two trials. However, in the first-line endocrine-sensitive setting, the combination of the mTOR antagonist temsirolimus with letrozole was no better than letrozole alone in the HORIZON trial,[20] suggesting that optimum endocrine treatment alone still has a role in the endocrine-naive or hormone-sensitive setting.

In conclusion, our results confirm that the use of an ER downregulator in the presence of potent oestrogen deprivation provides no advantage for women with hormone-receptor-positive breast cancer who have progressed on previous treatment with a NSAI. Alternative strategies of combined endocrine therapy with signalling inhibitors should be explored to overcome endocrine resistance to NSAIs.

Contributors

SRDJ was the chief investigator for the trial. SRDJ, DD, DC, AMW, AH, MD, and JMB developed the trial. SRDJ, LSK, DD, DC, AMW, AH, GC, MD, and JMB constituted the trial management group. SRDJ, PE, DD, DC, LH, Y-HI, JPB, AMB, K-LC, RJ, AR, AMW, DW, and AH were involved in recruitment, clinical care, and data returns. GC, NS, and H-JS coordinated the trial. EF and MD processed oestradiol samples. LSK did the main analyses, overseen by SRDJ and JMB. SRDJ and LSK wrote the first draft of the report and all other authors contributed to subsequent revision. All authors reviewed and approved the final version of the paper. The trial database was held at ICR-CTSU, where JMB had overall responsibility for trial coordination and statistical analyses.

Conflicts of interest

SRDJ and MD have received research funding and speaker honoraria from AstraZeneca. DC has received honoraria from AstraZeneca, Novartis, and Pfizer. AMB and K-LC have received honoraria from AstraZeneca. AMW has received honoraria from Roche, Celgene, Novartis, and Eisai. H-JS is employed by AstraZeneca. JMB has received research funding from AstraZeneca. The other authors declare that they have no conflicts of interest.

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