Cancer Chemother Pharmacol (2011) 67:223–230
DOI 10.1007/s00280-010-1483-x

CLINICAL TRIAL REPORT

Fulvestrant 250 mg versus anastrozole for Chinese patients with advanced breast cancer: results of a multicentre, double-blind, randomised phase III trial

Binghe Xu · Zefei Jiang · Zhimin Shao · Jiayu Wang · Jifeng Feng · Shuping Song · Zhendong Chen · Kangsheng Gu · Shiying Yu · Yiping Zhang · Chuan Wang · Fengchun Zhang · Junlan Yang

Received: 29 August 2010 / Accepted: 24 September 2010 / Published online: 12 October 2010

Abstract
Background and purpose Fulvestrant, an oestrogen receptor (ER) antagonist with no known agonist effects, has shown activity in postmenopausal patients with ER-positive advanced breast cancer recurring or progressing following prior endocrine therapy. This double-blind, double-dummy, randomised phase III study (NCT00327769) was designed to compare the efficacy and safety of fulvestrant versus anastrozole in advanced breast cancer of Chinese postmenopausal women whose disease has progressed following prior endocrine treatment.
Materials and methods A total of 234 patients were randomised to fulvestrant 250 mg/month ($n = 121$) or 1 mg/day anastrozole ($n = 113$), together with matching placebo. The primary endpoint was time to progression (TTP). Secondary endpoints included objective response rate (ORR), duration of response (DoR), clinical benefit rate (CBR) and time to treatment failure (TTF).
Results Baseline characteristics were similar, with the possible exception that a higher number of fulvestrant patients had received two prior chemotherapy regimens. Median TTP was 110 days in the fulvestrant group versus 159 days in the anastrozole group (hazard ratio [HR], 1.314; 95% confidence intervals [CI], 0.948, 1.822; $P = 0.101$). ORR was 10% in the fulvestrant group and 14% in the anastrozole group. Median DoR from randomisation to progression was 436 days versus 432 days for the fulvestrant and anastrozole groups, respectively. CBR for fulvestrant (36.1%) versus anastrozole (48.2%) was not statistically different between the groups. TTF (110 days versus 147 days for the fulvestrant and anastrozole groups, respectively) was not statistically different

B. Xu (✉) · J. Wang
Department of Medical Oncology, Cancer Hospital and Institute, Chinese Academy of Medical Sciences and Peking Union Medical College, No. 17 Panjiayuan Nanli, Chaoyang District, 100021 Beijing, China
e-mail: bhxu@hotmail.com

Z. Jiang
Beijing 307 Hospital, Beijing, China

Z. Shao
Cancer Hospital and Shanghai Cancer Institute, Fudan University, Shanghai, China

J. Feng
Jiangsu Cancer Hospital, Nanjing, China

S. Song
Shandong Cancer Hospital, Jinan, China

Z. Chen · K. Gu
First Affiliated Hospital, Anhui Medical University, Hefei, China

S. Yu
Tongji Hospital, Huizhong Science and Technique University, Wuhan, China

Y. Zhang
Zhejiang Cancer Hospital, Hangzhou, China

C. Wang
Affiliated Union Hospital, Fujian Medical University, Fuzhou, China

F. Zhang
Renji Hospital, Shanghai Jiaotong University, Shanghai, China

J. Yang
301 Hospital, Beijing, China

between the treatments (HR, 1.307; 95% CI, 0.961, 1.778; $P = 0.088$). Both treatments were well tolerated, with only two patients treated with fulvestrant and four patients treated with anastrozole withdrawn from study treatment due to adverse events.

Conclusions These data demonstrate that fulvestrant 250 mg and anastrozole were similarly effective and well tolerated in the treatment of postmenopausal Chinese women with advanced breast cancer whose disease had progressed or recurred on prior endocrine treatment.

Keywords Advanced breast cancer · Anastrozole · Arimidex · China · Faslodex · Fulvestrant · Oestrogen receptor

Introduction

Tamoxifen has been the mainstay of endocrine treatment for oestrogen receptor (ER)-positive postmenopausal advanced breast cancer for many years. However, third-generation aromatase inhibitors (AIs), including anastrozole, letrozole and exemestane, have since proved more effective and are now increasingly used ahead of tamoxifen in both the advanced and adjuvant settings [1–3].

Resistance to endocrine treatment will eventually lead to the disease progressing in most patients with advanced breast cancer. However, tumours often remain sensitive to subsequent endocrine therapy, so it is often standard practice that a different endocrine treatment will follow before that patient receives less tolerable cytotoxic chemotherapy. It is, therefore, important to develop new endocrine treatments that lack cross-resistance [4].

Tamoxifen is a non-steroidal anti-oestrogen, and it competes efficiently with oestrogen for binding to the ERs. However, it has partial agonist activity that leads to incomplete blockage of oestrogen-mediated activity and limits its effectiveness as well as unwanted side effects such as endometrial cancer when administered for long periods. Fulvestrant is a steroidal analogue of oestrogen which completely inhibits ER signalling. Unlike tamoxifen, it has no oestrogen agonist effects. Fulvestrant also has a novel mode of action since it binds, blocks and, unlike other therapies, accelerates degradation and loss of the ER. As a result, there is less chance of the ER being activated by alternative pathways (e.g. growth factor–mediated mechanisms) that are believed to cause resistance, which may delay the development of resistance [5].

Registration trials for fulvestrant 250 mg were conducted in Europe, South Africa and Australia (Trial 0020), and North America (Trial 0021), which compared the safety and efficacy of fulvestrant 250 mg versus anastrozole in postmenopausal women with advanced breast cancer whose disease had progressed on prior endocrine treatment [6, 7]. In both trials individually, and in a subsequent combined analysis [8], fulvestrant 250 mg demonstrated non-inferiority to anastrozole in terms of the primary endpoint of time to progression (TTP), which led to fulvestrant 250 mg being licensed for the treatment of postmenopausal women whose disease has progressed or recurred following prior anti-oestrogen therapy. Fulvestrant 250 mg gained FDA approval in 2002 and was licensed in Europe in 2004, but it is not currently approved for clinical use in China.

The present study compares the efficacy and tolerability of fulvestrant 250 mg versus anastrozole in postmenopausal Chinese women with advanced breast cancer whose disease has progressed following prior endocrine treatment.

Patients and methods

Study design

This was a phase III, double-blind, double-dummy, randomised, parallel-group study (NCT00327769), designed to compare the efficacy of fulvestrant 250 mg (monthly) with anastrozole 1 mg (daily). The study was conducted at 19 centres in China.

Patients

Eligible patients were postmenopausal women with ER-positive advanced breast cancer who had relapsed following previous adjuvant anti-oestrogen therapy or whose disease had progressed while on the first anti-oestrogen therapy for advanced disease. Metastatic or advanced disease not amenable to curative treatment was confirmed histologically or cytologically, and all patients had a World Health Organisation (WHO) performance status ≤ 2. Patients were defined as postmenopausal if they had undergone prior bilateral oophorectomy, were ≥ 60 years, were aged <60 years with amenorrhoea for ≥ 12 months or if follicle-stimulating hormone and plasma oestradiol levels were in the postmenopausal range.

Exclusion criteria included the following: the presence of life-threatening metastatic visceral disease or symptomatic pulmonary lymphangitic spread; more than one prior medical endocrine treatment for advanced disease; more than two prior chemotherapy regimens for advanced disease (two prior regimens were permitted); extensive radiation therapy or cytotoxic treatment within 4 weeks prior to screening; current or prior malignancy within previous 3 years (other than breast cancer or adequately treated basal cell or squamous cell carcinoma of the skin or in situ carcinoma or the cervix); treatment with a

non-approved or experimental drug within 4 weeks of randomisation; laboratory values indicating impaired liver or renal function; history of bleeding diathesis; or any severe concomitant condition or abnormal laboratory test result.

The study was performed in accordance with the Declaration of Helsinki and was consistent with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Good Clinical Practice. All patients gave written informed consent, and the relevant ethics committees approved the studies.

Study treatment

Patients were randomised 1:1 to receive fulvestrant 250 mg every 4 weeks via intramuscular injection with matching placebo to anastrozole once daily, or anastrozole 1 mg daily p.o. with matching placebo to fulvestrant monthly. Treatment continued until disease progression or any of the discontinuation criteria were met. Analyses of endpoints were performed when >50% patients had progressed or died.

Study assessments

The primary endpoint was TTP, which was defined as the time from randomisation to the time of objective disease progression or death from any cause. Secondary endpoints were as follows: objective response rate (ORR; the proportion of all treated patients with measurable disease at baseline who had a best objective tumour response of either complete response [CR] or partial response [PR]); duration of response (DoR; defined in two ways and assessed only in patients with an objective response; from the date of first documentation of objective response until disease progression or death due to any cause or from the date of randomisation until disease progression or death due to any cause); clinical benefit rate (CBR; the proportion of treated patients with measurable disease at baseline who had a best objective tumour response of CR plus PR plus stable disease ≥24 weeks); and time to treatment failure (TTF; the earliest occurrence of disease progression or withdrawal of study treatment for any reason, including death from any cause).

Adverse events (AEs) and serious adverse events (SAEs) were recorded at each visit and throughout the study; the relationship between the AEs/SAEs and treatment was determined by the study investigator. AEs and SAEs were classified by MedDRA (version 10 or above)-preferred term and system organ class and were graded according to the National Cancer Institute Common Terminology Criteria (CTC) version 3.0 for AEs. The most common AEs and the most common drug-related AEs are reported here.

Statistical analysis

The primary study endpoint, TTP, was summarised using Kaplan–Meier methodology, and the primary analysis was the logrank test to estimate median TTP. The estimate of treatment effect was compared using the hazard ratio [HR] of fulvestrant 250 mg to anastrozole together with 95% confidence intervals (CI) and *P*-value. A secondary analysis using the Cox proportional hazards model (including the covariates of performance status, measurable compared with non-measurable disease, cytotoxic chemotherapy for breast cancer, and current use of bisphosphonate therapy for bone disease) was also performed.

TTF was analysed in the same way as TTP. ORR was analysed using a logistic regression model with treatment factor only. Results were expressed as the odds ratio [OR] together with 95% CI and *P* value. DoR was summarised from both date of response to progression and date of randomisation to progression as a Kaplan–Meier estimate of median duration. Due to the small number of responding patients, no formal statistical evaluation was performed. As patients without measurable disease at baseline were not included in the analyses of ORR and CBR, summary of demographic performance status and median TTP was performed for these subjects.

No formal statistical analyses were performed on the safety data from this trial.

Analysis sets included the following: intention to treat (all randomised patients), per protocol (treated patients with no protocol violation) and safety (all randomised patients who received any study treatment).

Results

Patients

Of 242 enrolled patients, 234 met the eligibility criteria and were randomised 1:1 to receive fulvestrant 250 mg ($n = 121$) or anastrozole ($n = 113$) (Fig. 1). The first patient enrolled in the study on 7 November 2005, and the final subject completed the study on 10 September 2007. Baseline characteristics were comparable across both treatment groups, with the possible exception being the proportion of patients who had received two prior life-saving chemotherapy regimens: 32% and 24% for the fulvestrant 250 mg and anastrozole groups, respectively (Table 1). The study population was exclusively oriental with a mean age of 54.1 years. The majority of patients had a WHO performance status of 0 (76%) or 1 (20%), and the most frequent histology type was infiltrating ductal carcinoma (80%).

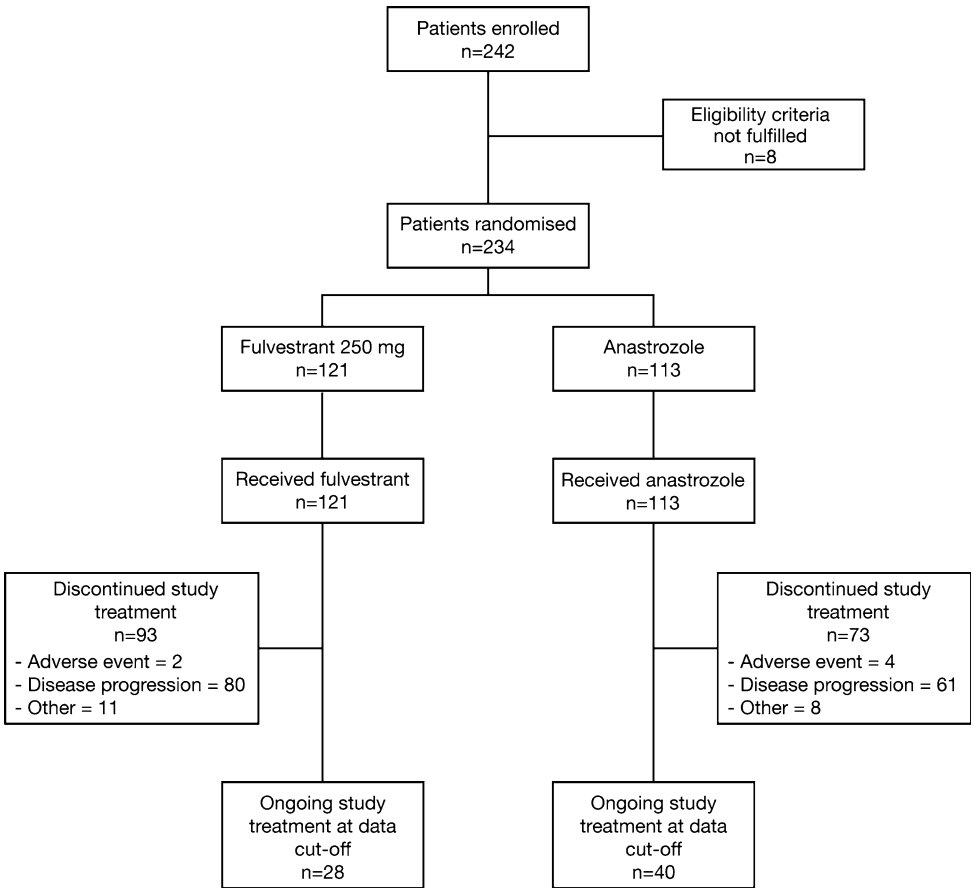

Fig. 1 CONSORT diagram

Efficacy

Analysis of the primary endpoint, TTP, revealed that there was no statistical difference between the treatment groups. However, there was a numerical advantage for anastrozole (Fig. 2). The median TTP was 110 days versus 159 days for the fulvestrant 250 mg and anastrozole treatment groups, respectively (HR, 1.314; 95% CI 0.948, 1.822; $P = 0.101$).

In the prospectively planned subgroup analysis for patients without measurable disease at baseline, median TTP was 124 days and 339 days for the fulvestrant 250 mg and anastrozole treatment groups, respectively (HR, 1.852; 95% CI 0.977, 3.898; $P = 0.058$) (Fig. 3a). In patients with measurable disease at baseline, median TTP was 110 days for the fulvestrant 250 mg group and 115 days for those patients receiving anastrozole (HR, 1.161; 95% CI 0.796, 1.693; $P = 0.438$) (Fig. 3b).

Fulvestrant 250 mg was not significantly different from anastrozole in terms of ORR, although the number of patient responders was slightly higher for anastrozole (14%) than for fulvestrant 250 mg (10%) [OR, 0.631; 95% CI 0.244, 1.635; $P = 0.343$]. The median DoR from randomisation to progression was 436 days for the fulvestrant 250 mg group and 432 days for the anastrozole group.

CBR was slightly higher with fulvestrant 250 mg than with anastrozole (48.2% versus 36.1% for fulvestrant 250 mg and anastrozole, respectively), although this difference was not significant (OR, 0.608; 95% CI 0.327, 1.133; $P = 0.117$).

In terms of TTF, there was no significant difference between the treatment groups, although there was a numerical advantage for anastrozole. Median TTF was 110 days for the fulvestrant 250 mg group and 147 days for the anastrozole group (HR, 1.307; 95% CI 0.961, 1.778; $P = 0.088$) (Table 2).

Safety/tolerability

Mean duration of exposure to treatment was 152.3 days for the fulvestrant 250 mg group and 174.3 days for the anastrozole group.

A total of 332 AEs were reported by 89 (38%) of the 234 patients in the study. The most commonly reported AEs were asthenia (fulvestrant 250 mg versus anastrozole: 14 versus 12), nausea (8 versus 3) and injection-site pain (5 versus 9) (Table 3). Frequency of injection-site reactions, including injection-site anaesthesia, pain, pruritus and swelling, was similar between the two treatment groups, with 8 incidences (7%) reported in the fulvestrant

Table 1 Demographic and baseline characteristics

	Fulvestrant 250 mg ($n = 121$)	Anastrozole ($n = 113$)
Age (years)		
Mean (SD)	53.4 (8.3)	54.8 (9.8)
Range	33–78	31–77
Body mass index		
Mean (SD)	24.5 (3.3)	24.1 (3.8)
Range	17.6–37.4	15.4–33.0
Measurable disease at baseline, *n* (%)	83 (69)	83 (73)
Histology type, *n* (%)		
Infiltrating ductal carcinoma	97 (80)	90 (80)
Infiltrating lobular carcinoma	9 (7)	10 (9)
Medullary	1 (1)	1 (1)
Paget's	1 (1)	0 (0)
Other	13 (11)	12 (11)
WHO performance status, *n* (%)		
0	89 (74)	89 (79)
1	27 (22)	19 (17)
2	5 (4)	5 (4)
Number of previous life-saving chemotherapy regimens, *n* (%)		
1	42 (68)	37 (76)
2	20 (32)	12 (24)

SD standard deviation, *WHO* World Health Organisation

250 mg group and 10 (9%) reported in the anastrozole group; all injection-site reactions were CTC grade 1.

The most common treatment-related AEs were asthenia (fulvestrant 250 mg versus anastrozole: 13 versus 11), injection-site pain (5 versus 9) and hot flush (5 versus 4). Treatment-related AEs were typically CTC grade 1, with a small number of grade 2 events. One patient in the anastrozole group reported one grade 3 treatment-related AE (increased gamma-glutamyltransferase), while no grade 4/5 AEs were recorded.

The incidence of SAEs was 5 (4%) with fulvestrant 250 mg and 6 (5%) with anastrozole. One SAE led to death in the fulvestrant 250 mg group (respiratory failure), and four SAEs led to death in the anastrozole group (lung infection, death, renal failure and asphyxia), but these were not determined to be due to the study treatment (Table 4).

Two patients in the fulvestrant 250 mg group and four patients in the anastrozole group withdrew from the study due to an AE. These were due to respiratory failure and decreased platelet count in the fulvestrant 250 mg group, and asphyxia, lung infection, renal failure and death (determined to be due to hydroelectric disturbance) in the anastrozole group. Decreased platelet count in one patient in the fulvestrant 250 mg group was the only treatment-related AE that led to the discontinuation of treatment. There were no clinically important changes in haematological, clinical chemistry or urinalysis variables with either treatment.

Discussion

This was a double-blind comparison of fulvestrant 250 mg versus anastrozole 1 mg in postmenopausal women in China with advanced breast cancer whose disease had progressed or relapsed on prior endocrine therapy. In terms of the primary endpoint analysis of TTP, there was no significant difference between the two treatment groups. There were also no statistically significant differences between the study arms in terms of ORR, CBR and TTF. Due to the small numbers of responders, no conclusions were possible for DoR.

While not statistically significant, there was a numerical advantage in terms of TTP for anastrozole, which was unexpected given the similarities between this study and

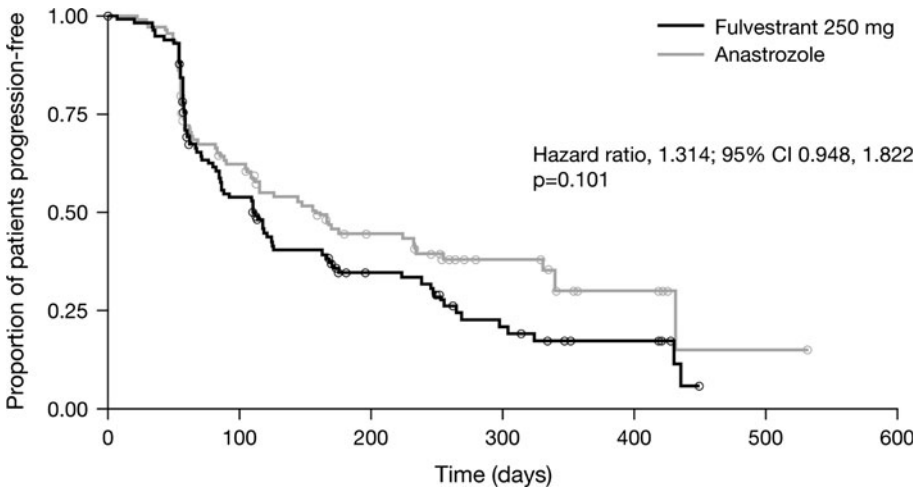

Fig. 2 Kaplan–Meier estimates for time to progression: all subjects. *CI* confidence interval

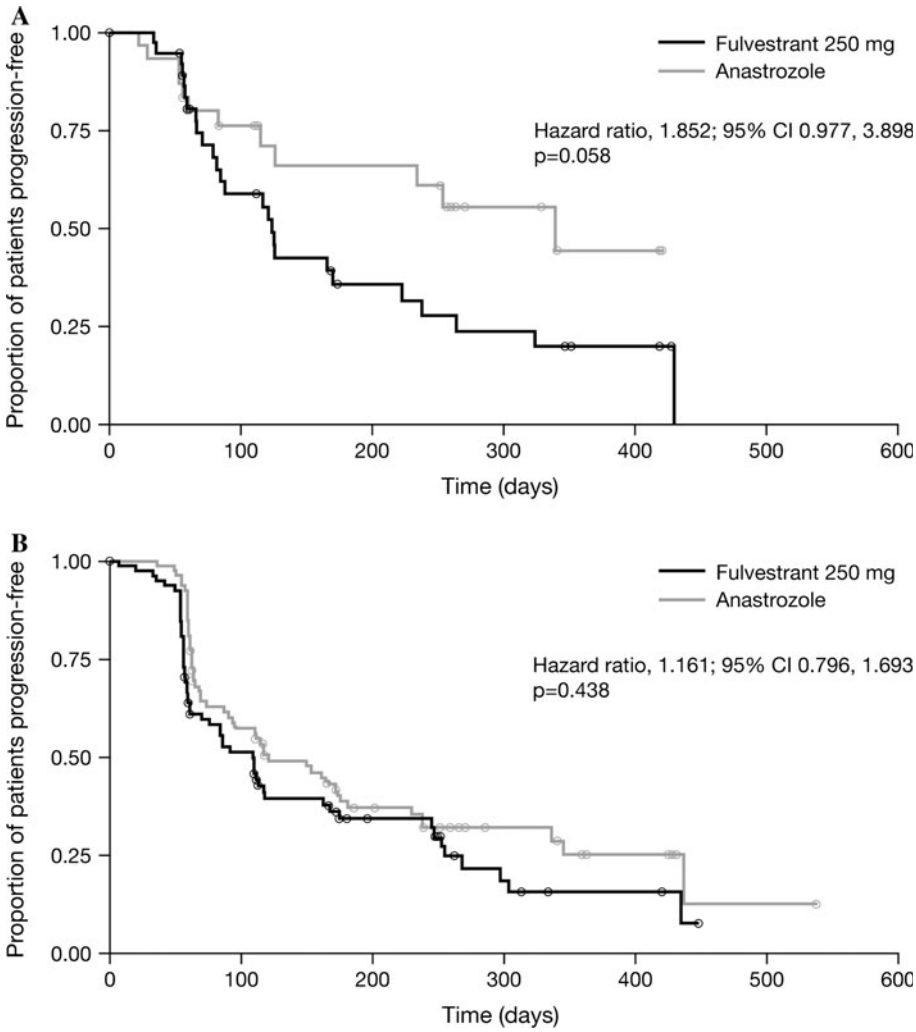

Fig. 3 **a** Kaplan–Meier estimates for time to progression: subjects with no measurable disease at baseline. **b** Kaplan–Meier estimates for time to progression: subjects with measurable disease at baseline. *CI* confidence interval

Table 2 Secondary endpoint results

Endpoint	Fulvestrant 250 mg	Anastrozole
Time to treatment failure (TTF)	$n = 121$	$n = 113$
TTF (median) (days)	110	147
Clinical benefit rate (CBR)	$n = 83$	$n = 83$
Best response, *n* (%)		
Complete response (CR)	1 (1)	0 (0)
Partial response (PR)	7 (8)	12 (14)
Stable disease (SD) $\geq$ 24 weeks	22 (27)	28 (34)
CBR (CR + PR + SD $\geq$ 24 weeks)	30 (36.1)	40 (48.2)
Objective response rate (ORR)	$n = 83$	$n = 83$
Number of responders (CR + PR combined), *n* (%)	8 (10)	12 (14)
Duration of response (DoR)	$n = 8$	$n = 12$
Mean DoR from date of response (median) (days)	266	376
Mean DoR from randomisation (median) (days)	436	432

TTF, CBR and ORR were summarised from the intent-to-treat analysis set; CBR and ORR were determined from all patients treated with measurable disease at baseline; DoR was determined from the subset of patients responding

the previously reported Trials 0020 and 0021. Trials 0020 (randomised, open-label trial, conducted in Europe, South Africa and Australia) and 0021 (double-blind, double-dummy trial, conducted in North America) both demonstrated individually that fulvestrant 250 mg was at least as effective as anastrozole in the same setting [6, 7].

Table 3 Most commonly reported adverse events (≥3% in total; safety analysis set)

Adverse event, *n* (%)	Fulvestrant 250 mg ($n = 121$)	Anastrozole ($n = 113$)
Asthenia	14 (12)	12 (11)
Injection-site pain	5 (4)	9 (8)
Nausea	8 (7)	3 (2)
Hot flush	5 (4)	4 (3)
Back pain	1 (1)	7 (6)
Cough	5 (4)	3 (3)
Pain in extremity	4 (3)	4 (3)
Pyrexia	5 (4)	3 (3)
Hyperhidrosis	5 (4)	2 (2)
Arthralgia	5 (4)	1 (1)
Hypoaesthesia	5 (4)	1 (1)
Anorexia	4 (3)	0 (0)

Table 4 Number of subjects who had an adverse event in any category (safety analysis set)

	Fulvestrant 250 mg ($n = 121$) *n* (%)	Anastrozole ($n = 113$) *n* (%)
Any AE	48 (40)	41 (36)
Any study-treatment-related AE	32 (26)	25 (22)
Any SAE	5 (4)	6 (5)
Any SAE leading to death	1 (1)	4 (4)
Any SAE not leading to death	4 (3)	3 (3)
Any study-treatment-related SAE	2 (2)	0 (0)
Discontinuations due to AEs	2 (2)	4 (4)
Other significant AE	3 (2)	0 (0)

Patients with multiple events in the same category are counted only once in that category. Patients in more than one category are counted once in each of those categories

AE adverse event, *SAE* serious adverse event

A prospective combined analysis of both trials showed fulvestrant 250 mg to be numerically superior to anastrozole in terms of TTP, with estimated median TTP values of 5.5 months and 4.1 months for the fulvestrant 250 mg and anastrozole groups, respectively (HR, 0.95; 95% CI, 0.82, 1.10; $P = 0.48$). ORR was also numerically in favour of fulvestrant 250 mg in these trials.

The P value for treatment comparison of TTP was $P = 0.101$, which indicates that if there was truly no difference between fulvestrant 250 mg and anastrozole, one in ten studies would show a result this extreme or greater. Compared with Trial 0020 ($n = 451$) and 0021 ($n = 400$), the present study was small ($n = 234$). The relatively limited sample size meant that this study was more vulnerable to sampling bias, and it is likely that the small size contributed to any variability between the three studies.

Within the present study, although most baseline characteristics were largely comparable, more patients in the fulvestrant 250 mg group (32%) than in the anastrozole group (24%) had undergone two previous rounds of chemotherapy, potentially giving those patients in the fulvestrant 250 mg group a worse prognosis. Additionally, TTP for anastrozole appeared better in terms of those patients without measurable disease at the start of the treatment, but the two treatments were similar in those patients with measurable disease at baseline. TTP for patients with no measurable disease at baseline was 339 days for the anastrozole group, more than double the time that was expected for the anastrozole group based on findings in Trials 0020/0021. However, these differences in baseline characteristics are not considered of sufficient clinical relevance as to be able to change the comparison between fulvestrant 250 mg and anastrozole.

It is unlikely that differences between the present study and Trials 0020/0021 may be due to differences in geographic background. Pharmacokinetic data from Trials 0020/0021 (conducted in Europe, South Africa, Australia and North America) and a separate trial of Japanese women found no differences in fulvestrant plasma pharmacokinetic profiles, regardless of racial/ethnic origin [9, 10].

Overall, both treatments were well tolerated, and the proportion of patients experiencing AEs was similar across treatment groups. AEs were predominantly grade 1 or 2 and known to be associated with hormone therapy for breast cancer, a consequence of the underlying breast cancer, postmenopausal status or other concurrent medical conditions. The most frequently reported AEs were asthenia, nausea and injection-site pain. There were very few AEs leading to death (one versus four for the fulvestrant 250 mg and anastrozole groups, respectively), and none of these were determined by the study investigator to be causally related to the study treatment. Only two patients in the fulvestrant 250 mg group (2%) and four in the anastrozole group (4%) discontinued treatment due to an AE, and only one of these (in the fulvestrant 250 mg group) was determined to be treatment-related.

The traditional endocrine treatment for postmenopausal women with hormone receptor–positive breast cancer has been tamoxifen. However, since improved efficacy was demonstrated and guidelines were subsequently changed in 2005, AIs such as anastrozole are now increasingly used ahead of tamoxifen in the advanced and adjuvant settings [11]. Unfortunately, most patients with advanced disease will eventually progress, so there is a requirement for new agents without cross-resistance. Due to its distinct mode of action and compelling clinical trial data, fulvestrant 250 mg offers an attractive treatment option in the endocrine sequence for postmenopausal women with

ER-positive advanced breast cancer whose disease has progressed or recurred on prior endocrine therapy.

Acknowledgments We thank Simon Vass, PhD, from Complete Medical Communications who provided medical writing support funded by AstraZeneca. We also thank Dr. Tao Huang (Union Hospital, Huazhong Science and Technique University), Dr. Jun Ren (Cancer Hospital, Peking University), Dr. Gang Cheng (Beijing Hospital), Dr. Jiwei Liu (First Affiliated Hospital, Dalian Medical University), Dr. Chunkang Yang and Dr. Jianxin Ye (First Affiliated Hospital, Fujian Medical Unversity), Dr. Ning Liao (Guandong Province Hospital), Dr. Wenchao Liu (Xijing Hospital) and Dr. Shukui Qin (Nanjing Bayi Hospital) for their dedication to this study.

Conflict of interest Binghe Xu, Zefei Jiang, Zhimin Shao, Jiayu Wang, Jifeng Feng, Shuping Song, Zhendong Chen, Kangsheng Gu, Shiying Yu, Yiping Zhang, Chuan Wang, Fengchun Zhang, Junlan Yang have nothing to declare.

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