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CLINICAL TRIAL

Fulvestrant 500 mg versus anastrozole 1 mg for the first-line treatment of advanced breast cancer: follow-up analysis from the randomized 'FIRST' study

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Abstract Fulvestrant fIRst-line Study comparing endocrine Treatments is a phase II, randomized, open-label study comparing fulvestrant 500 mg with anastrozole 1 mg as first-line endocrine therapy for postmenopausal women with hormone receptor-positive (HR+) advanced breast cancer. At data cut-off, only 36 % of patients had progressed and the median time to progression (TTP) had not been reached for fulvestrant. Here, we report follow-up data for TTP for fulvestrant 500 mg versus anastrozole 1 mg. Key inclusion criteria were postmenopausal women with estrogen receptor-positive and/or progesterone receptor-positive locally advanced or metastatic breast cancer and no prior endocrine therapy. Key exclusion criteria were presence of life-threatening metastases and prior treatment with a non-approved drug. Fulvestrant was administered 500 mg/month plus 500 mg on day 14 of month 1; anastrozole was administered 1 mg/day. TTP was defined by modified Response Evaluation Criteria in Solid Tumors v1.0 before data cut-off for the primary analysis, and investigator opinion after data cut-off. Best overall response to subsequent therapy and serious adverse events are also reported. In total, 205 patients received fulvestrant 500 mg ($n = 102$) or anastrozole ($n = 103$). Follow-up analysis was performed when 79.5 % of patients had discontinued study treatment. Median TTP was 23.4 months for fulvestrant versus 13.1 months for anastrozole; a 34 % reduction in risk of progression (hazard ratio 0.66; 95 % confidence interval: 0.47, 0.92; $P = 0.01$). Best overall response to subsequent therapy and clinical benefit rate for subsequent endocrine therapy was similar between the treatment groups. No new safety concerns for fulvestrant 500 mg were documented. These longer-term, follow-up results confirm efficacy benefit for fulvestrant 500 mg versus anastrozole as first-line endocrine therapy for HR+ advanced breast cancer in terms of TTP, and, importantly, show similar best overall response rates to subsequent endocrine therapy.

Keywords Advanced breast cancer · Anastrozole · Fulvestrant 500 mg · Hormone receptor-positive · Time to progression

Abbreviations

AE	Adverse event
AI	Aromatase inhibitor
CBR	Clinical benefit rate

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CI	Confidence interval
CONFIRM	COmparisoN of Faslodex In Recurrent or Metastatic breast cancer
DoCB	Duration of clinical benefit
DoR	Duration of response
ER	Estrogen receptor
FINDER	Faslodex InvestigatioN of Dose evaluation in Estrogen Receptor-positive advanced breast cancer (FINDER)
FIRST	Fulvestrant fIRst-line Study comparing endocrine Treatments
HR	Hormone receptor
ORR	Objective response rate
NEWEST	Neoadjuvant Endocrine therapy for Women with Estrogen-Sensitive Tumors
PFS	Progression-free survival
PgR	Progesterone receptor
PK	Pharmacokinetic
RECIST	Response Evaluation in Solid Tumors
SAE	Serious adverse event
TTF	Time to treatment failure
TTP	Time to progression
WHO-PS	World Health Organization-Performance Status

Introduction

Endocrine therapy is a standard first-line treatment option for advanced breast cancer in postmenopausal women with hormone receptor-positive (HR+) disease. The third-generation aromatase inhibitors (AIs) letrozole and anastrozole have demonstrated improved time to progression (TTP) and tolerability compared with tamoxifen, and are now considered the standard treatment in this setting [2, 8, 9].

Fulvestrant is a pure antiestrogen that binds directly to the estrogen receptor (ER) in a mechanism of action distinct from other endocrine therapies for breast cancer [21]. At the monthly 250 mg dose, fulvestrant is at least as effective as anastrozole for the second-line treatment of postmenopausal women with advanced breast cancer [5, 11, 16]. However, at this dose, fulvestrant was not associated with improved efficacy when compared with tamoxifen in the first-line setting [4].

Early clinical data and results of pharmacokinetic (PK) modeling suggested that the efficacy of fulvestrant could be increased with a higher dosing regimen [15, 17]. This was demonstrated in the phase III COmparisoN of Faslodex In Recurrent or Metastatic breast cancer (CONFIRM) trial, which showed that fulvestrant 500 mg significantly prolonged progression-free survival (PFS), the primary study endpoint, with no detrimental effects on tolerability or quality of life. This meant that fulvestrant 500 mg was associated with a greater benefit-risk profile compared with fulvestrant 250 mg for the treatment of postmenopausal women with locally advanced or metastatic breast cancer following failure of prior antiestrogen therapy [3].

Fulvestrant fIRst-line Study comparing endocrine Treatments (FIRST) is a phase II, randomized, open-label, multicenter, parallel-group study designed to compare fulvestrant 500 mg with anastrozole 1 mg in the first-line setting for the treatment of advanced breast cancer (ClinicalTrials.gov identifier NCT00274469). Findings from this study showed that fulvestrant was at least as effective as anastrozole in terms of the primary endpoint of clinical benefit rate (CBR) and objective response rate (ORR) [19]. Data cut-off for the primary analysis was performed 6 months after the last patient was randomized. At this time, 117 (57.1 %) patients were still receiving study treatment and only 35.6 % of patients had progressed [30 patients (29.4 %) in the fulvestrant and 43 patients (41.7 %) in the anastrozole group]. The median TTP had not been reached for fulvestrant compared with 12.5 months for anastrozole [hazard ratio 0.63; 95 % confidence interval (CI): 0.39, 1.00; $P = 0.0496$] [19].

A more mature follow-up analysis of TTP was therefore planned for when approximately 75 % of patients had discontinued therapy. Here, we report findings from this analysis.

Methods

Study design and patients

The methods have been described elsewhere [19] and are described briefly here. Patients were randomized to receive fulvestrant 500 mg (500 mg/month intramuscularly plus 500 mg on day 14 of month 1) or anastrozole (1 mg/day orally). Treatment continued until disease progression or any other discontinuation event.

The study population comprised postmenopausal women with ER-positive (ER+) and/or progesterone receptor-positive (PgR+) locally advanced or metastatic breast cancer who had not received any prior endocrine therapy for locally advanced or metastatic disease. Previous endocrine therapy for early disease completed more than 12 months before randomization was permitted. Patients had to have measurable disease, as confirmed by Response Evaluation Criteria in Solid Tumors v1.0 (RECIST) [20], or bone lesions with a lytic component. Key exclusion criteria included the presence of life-threatening metastases, prior treatment with a non-approved drug,

abnormal laboratory test values, and a history of bleeding diatheses.

Randomization and masking

Patients were randomized sequentially using randomization cards. The clinical study team were unaware of the randomization scheme until the data had been collected and locked for primary analysis. To prevent biasing the results of the tumor assessments, a blinded independent review was performed by a radiologist at BioImaging Technologies (Leiden, The Netherlands). Other post hoc analyses were performed by the Biostatistics department at AstraZeneca.

Efficacy analysis

The primary study endpoint was CBR; secondary endpoints included ORR, TTP, duration of clinical benefit (DoCB), and duration of response (DoR). CBR, ORR, DoCB, and DoR were not assessed in the follow-up period. Both CBR and TTP were relevant endpoints for this study; CBR allowed comparison of de novo response and progression rates but not assessment of acquired resistance.

This follow-up analysis was planned for when 75 % of patients had discontinued (failed) study treatment, with final analysis of data being performed within 12 months of the last patient discontinuing their randomized treatment. As this was a phase II trial, no formal adjustments were made for multiple testing. TTP was defined as the date from randomization to progression. For patients who progressed before the primary data cut-off, the date of progression, as determined by modified RECIST criteria, was already available. "Modified" RECIST relates to those patients with non-measurable disease at baseline, who had bone lesions with a lytic component, where progression of lytic bone lesions was regarded as a progression event. For patients who progressed after the data cut-off for the primary analysis, TTP was determined by investigator opinion.

Time to treatment failure (TTF) was also evaluated; defined as the time from randomization to cessation of trial therapy. For patients who stopped treatment before the primary data cut-off, this date was already available. For patients who stopped treatment after the primary data cut-off, the date of cessation of trial therapy was recorded on the case report form as the date that the last dose of drug was administered. As fulvestrant 500 mg is administered monthly, it is possible that the decision to discontinue treatment may have occurred at any point between the last injection and the next intended injection 28 days later. Therefore, TTF was calculated for fulvestrant as the date of last injection plus 14 days, representing the midpoint between scheduled treatment visits. In a post hoc analysis, TTF was calculated for fulvestrant as the date of the next intended injection (the date of the patient's last injection plus 28 days). This analysis was performed because most patients with advanced breast cancer have their treatment changed at a scheduled clinic visit.

Best overall response to first subsequent breast cancer therapy was determined by investigator opinion.

Tolerability

World Health Organization-Performance Status (WHO-PS) and serious adverse events (SAEs) were reported for fulvestrant and anastrozole throughout the follow-up period.

Statistics

The full analysis set included all randomized patients and was used to analyze efficacy. The safety analysis set included patients who received treatment after the data cut-off for the primary analysis.

For the analysis of TTP and TTF, Kaplan–Meier plots were generated. Hazard ratios, 95 % CIs, and P values were calculated using a log-rank test, unadjusted for baseline covariates.

A secondary analysis of TTP and TTF was also conducted. This was calculated using a Cox proportional hazards regression model and was adjusted for treatment and baseline covariates, including age (<65 vs. ≥65 years), hormone receptor status (both ER+ and PgR+ vs. not both ER+ and PgR+), visceral involvement (yes vs. no), prior chemotherapy (yes vs. no), and the presence or absence of measurable disease. A global interaction test using a 1 % significance level was performed to determine whether the overall treatment benefit was consistent across each of the baseline covariates.

Results

Patients

In total, 205 patients received fulvestrant ($n = 102$) or anastrozole ($n = 103$) (Fig. 1). Baseline demographics and disease characteristics were well balanced between the treatment groups. The primary study endpoint, CBR, was 72.5 % in the fulvestrant group compared with 67.0 % in the anastrozole group (odds ratio 1.30; 95 % CI: 0.72, 2.38; $P = 0.386$) [19]. The data cut-off for this follow-up analysis was March 26, 2010. At this point, 163 (79.5 %) patients had discontinued study treatment. Median duration of follow-up for TTP was 18.8 months in the fulvestrant group and 12.9 months in the anastrozole group.

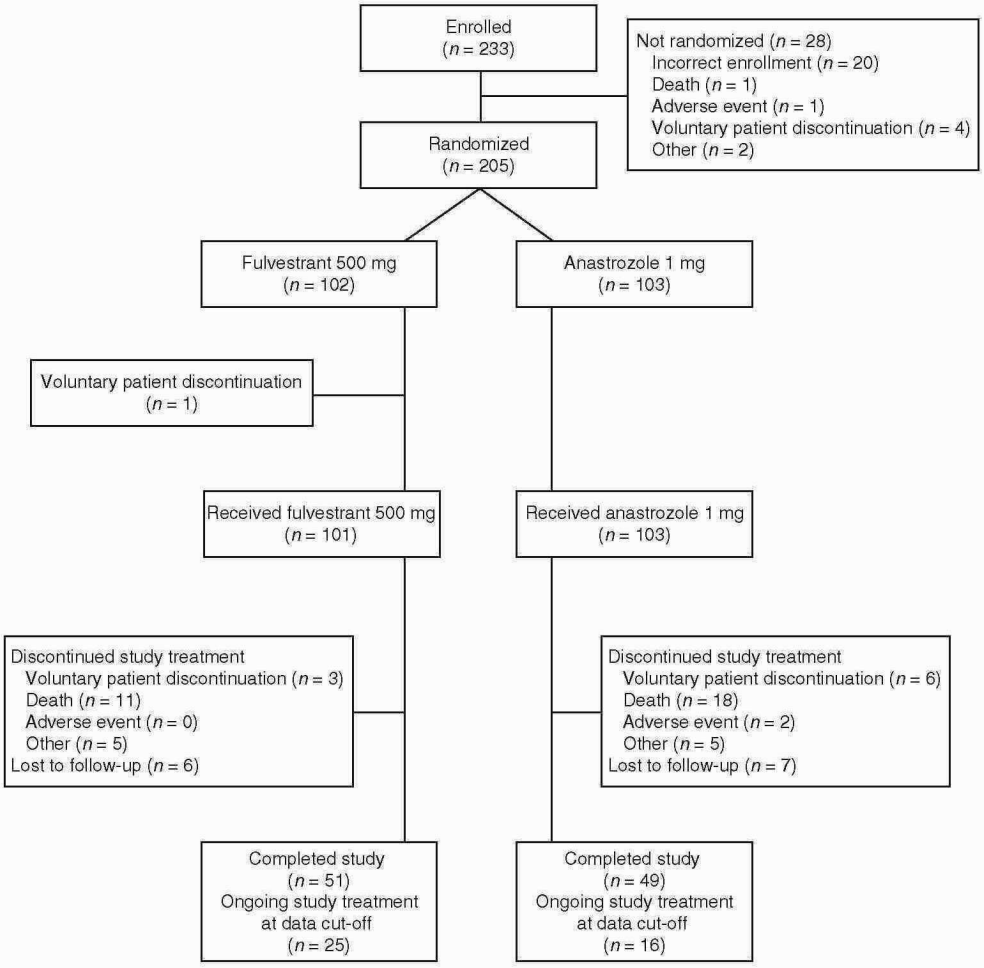

Fig. 1 CONSORT diagram

Efficacy

At the time of the follow-up analysis, 142 (69.3 %) patients had progressed; 63 (61.8 %) in the fulvestrant group compared with 79 (76.7 %) in the anastrozole group. Median TTP was 23.4 months for the fulvestrant group versus 13.1 months for the anastrozole group (hazard ratio 0.66; 95 % CI: 0.47, 0.92; $P = 0.01$), corresponding to a 34 % reduction in risk of progression (Fig. 2).

The difference in TTP was also statistically significant when adjusted for pre-defined covariates (hazard ratio 0.64; 95 % CI: 0.46, 0.90; $P = 0.01$). The global interaction test was not significant ($P = 0.34$). A forest plot representing TTP according to the pre-defined covariates is shown in Fig. 3, demonstrating that the treatment effect is consistent across all subgroups.

The number of patients who failed treatment in the fulvestrant group was 76 (74.5 %) compared with 87 (84.5 %) in the anastrozole group. Median TTF was 17.6 months for the fulvestrant group versus 12.7 months for the anastrozole group (hazard ratio 0.73; 95 % CI: 0.54, 1.00; $P = 0.05$), calculated by adding 14 days to the last fulvestrant injection (Fig. 4). The difference in TTF also remained consistent when adjusted for pre-defined covariates (hazard ratio 0.72; 95 % CI: 0.52, 0.98; $P = 0.04$). The global interaction test was not significant ($P = 0.31$). In the post hoc analysis with 28 days added to the last fulvestrant injection, median TTF was 18.1 months in the fulvestrant group versus 12.7 months for the anastrozole group (hazard ratio 0.71; 95 % CI: 0.52, 0.96; $P = 0.03$).

Subsequent breast cancer treatment was recorded for 64 patients in the fulvestrant group and 69 patients in the anastrozole group. In terms of best overall response to any subsequent systemic breast cancer therapy, 15 patients (23.4 %) in the fulvestrant group and 15 patients (21.7 %) in the anastrozole group achieved either a complete or partial response to subsequent therapy. CBR to first subsequent systemic therapy (complete response, partial response, or stable disease for ≥24 weeks) was 43.8 % (28/64 patients) in the fulvestrant group compared with 46.4 % (32/69 patients) in the anastrozole group (Table 1). Best response to subsequent endocrine therapy

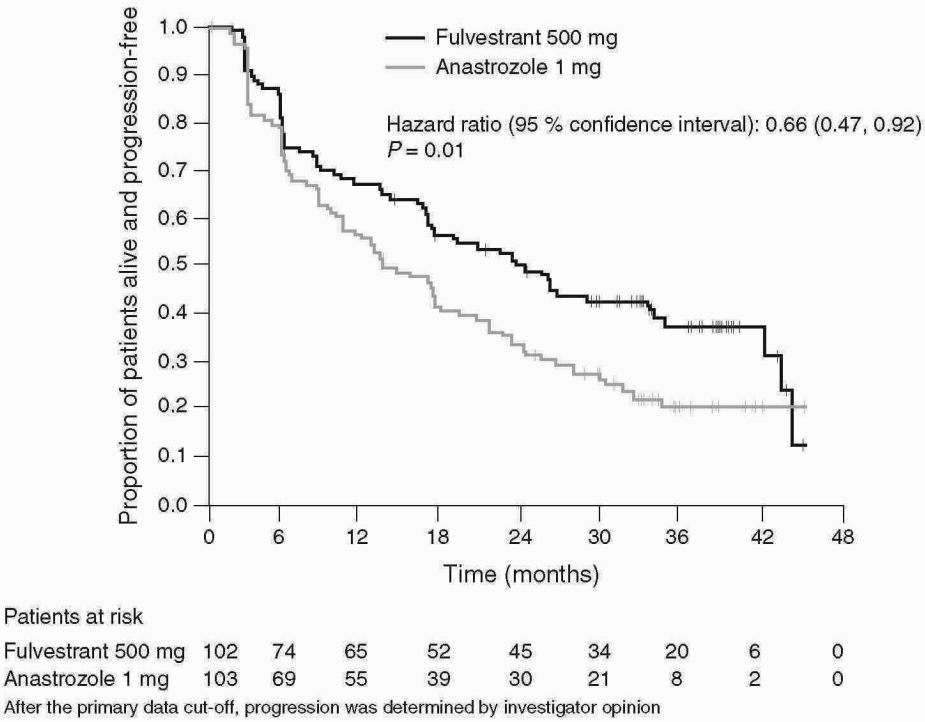

Fig. 2 Time to progression (full analysis set)

After the primary data cut-off, progression was determined by investigator opinion

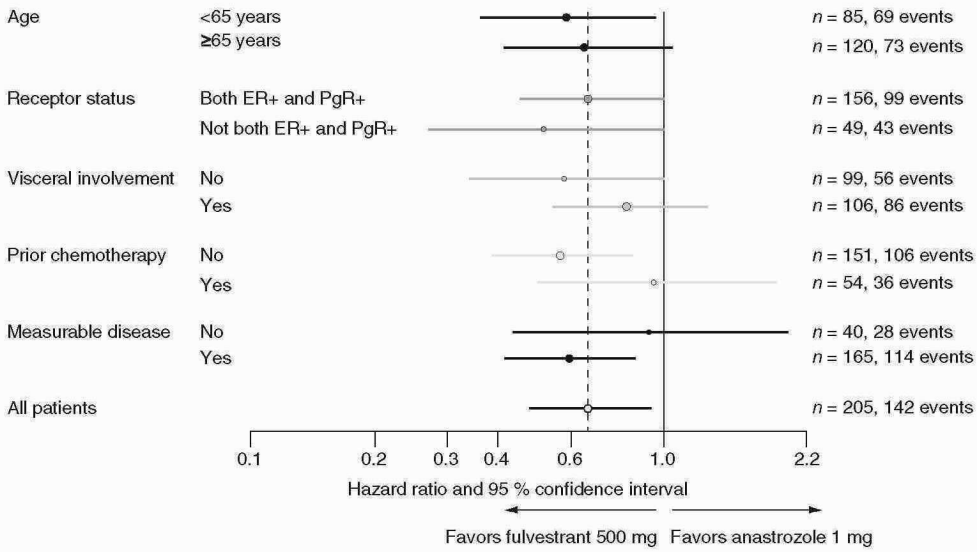

Fig. 3 Time to progression by pre-defined covariates (full analysis set)

ER estrogen receptor, *PgR* progesterone receptor

for breast cancer was also similar between the treatment groups. CBR to subsequent endocrine therapy for breast cancer was 41.2 % (14/34 patients) in the fulvestrant group and 42.0 % (21/50 patients) in the anastrozole group (Table 1).

Tolerability

Twelve SAEs were reported in seven patients in the fulvestrant group and 10 SAEs were reported in seven patients in the anastrozole group during the period after the primary data cut-off. Each SAE by preferred term was only reported in one patient. One SAE (pulmonary embolism) was considered treatment-related by the investigator in the fulvestrant group. No treatment-related SAEs were reported in the anastrozole group.

There were no clinically important differences in terms of WHO-PS. At each evaluation, the majority (>50 % in both treatment groups) of patients still receiving treatment had a PS of either 0 or 1.

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