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ARTICLE

Final Overall Survival: Fulvestrant 500 mg vs 250 mg in the Randomized CONFIRM Trial

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Background At the time of the initial analysis of overall survival (OS) for the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) randomized, double-blind, phase III trial, approximately 50% of patients had died. A final analysis of OS was subsequently planned for when 75% of patients had died.

Methods Patients were randomly assigned 1:1 to fulvestrant 500 mg administered as two 5-mL intramuscular injections on days 0, 14, and 28 and every 28 (±3) days thereafter or fulvestrant 250 mg administered as two 5-mL intramuscular injections (one fulvestrant and one placebo [identical in appearance to study drug]) on days 0, 14 (two placebo injections only), and 28 and every 28 (±3) days thereafter. OS was analyzed using an unadjusted log-rank test. No adjustments were made for multiplicity. Serious adverse events (SAEs) and best response to subsequent therapy were also reported. All statistical tests were two-sided.

Results In total, 736 women (median age = 61.0 years) were randomly assigned to fulvestrant 500 mg (n = 362) or 250 mg (n = 374). At the final survival analysis, 554 of 736 (75.3%) patients had died. Median OS was 26.4 months for fulvestrant 500 mg and 22.3 months for 250 mg (hazard ratio = 0.81; 95% confidence interval = 0.69–0.96; nominal $P = .02$). There were no clinically important differences in SAE profiles between the treatment groups; no clustering of SAEs could be detected in either treatment group. Type of first subsequent therapy and objective responses to first subsequent therapy were well balanced between the two treatment groups.

Conclusions In patients with locally advanced or metastatic estrogen receptor–positive breast cancer, fulvestrant 500 mg is associated with a 19% reduction in risk of death and a 4.1-month difference in median OS compared with fulvestrant 250 mg. Fulvestrant 500 mg was well tolerated, and no new safety concerns were identified.

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Fulvestrant is a pure estrogen receptor (ER) antagonist devoid of the agonistic properties displayed by tamoxifen in some tissues (1–4). After phase III studies, which demonstrated similar efficacy and an acceptable safety profile for fulvestrant 250 mg compared with anastrozole (1,5), fulvestrant 250 mg was approved as treatment in postmenopausal women with advanced hormone receptor–positive breast cancer that had progressed or recurred after prior antiestrogen therapy. However, previous preoperative studies showed that short-term exposure to fulvestrant was associated with a dose-dependent reduction in the levels of ER, progesterone receptor, and the cell proliferation–related antigen Ki67 (6,7) for fulvestrant doses up to 250 mg. Other phase I and phase III studies also suggested a dose–response effect for fulvestrant (1,5,8).

The phase III Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) trial compared the then-approved dose and dosing schedule of fulvestrant (250 mg every 28 days) with a higher-dose regimen (500 mg every 28 days plus an additional 500 mg on day 14 of the first month only) in postmenopausal women with locally advanced or metastatic ER-positive breast cancer that had recurred or progressed after prior endocrine therapy. The initial results showed that fulvestrant 500 mg was associated with a statistically significant increase in progression-free survival (PFS) without increased toxicity, therefore corresponding to a clinically meaningful improvement in benefit vs risk compared with fulvestrant 250 mg (9). Based on these data, the 500-mg dose of fulvestrant is now the approved dose in the European Union (approved in March 2010), United States (approved in September 2010), Japan (approved in November 2011), and other countries worldwide.

In the CONFIRM study, the assessment of the therapeutic efficacy of both doses of fulvestrant was evaluated by several secondary outcome measures, including overall survival (OS). At the time of the initial analysis, approximately 50% of patients had died. After the reporting of the 50% survival data, which showed a trend in favor of 500 mg over 250 mg, it was agreed to perform a final survival analysis after 75% of patients had died. Here we report the results of this final OS analysis.

Methods

Study Design and Patients

The CONFIRM study design, including eligibility criteria, exclusion criteria, and the calculation of sample size, has been described in detail elsewhere (9). Briefly, CONFIRM was a randomized, phase III, double-blind trial that evaluated two different doses of fulvestrant (500 mg vs 250 mg) in postmenopausal patients who had either locally advanced or metastatic ER-positive breast cancer (ClinicalTrials.gov identifier: NCT00099437; http://www.clinicaltrials.gov/ct2/show/NCT00099437). The primary study endpoint was PFS (the time elapsing between the date of randomization and the date of earliest evidence of objective disease progression or death from any cause). Secondary endpoints included objective response rate, clinical benefit rate, duration of response, duration of clinical benefit, OS, tolerability, and quality of life (9).

After initial analysis, all patients, regardless of whether they were still receiving randomized treatment, entered a survival follow-up phase. Patients remaining on randomized treatment during this follow-up phase continued on blinded randomized treatment until progression and were assessed for serious adverse events (SAEs) and survival status. Patients who had discontinued randomized treatment were assessed for their survival status and best response to their first subsequent systemic breast cancer therapy received after treatment discontinuation.

Ethics

The study was performed in accordance with the Declaration of Helsinki, consistent with International Conference on Harmonisation/Good Clinical Practice requirements. All patients gave written informed consent before study entry, and the study protocol was approved by the institutional review board of each participating institution.

Randomization and Masking

Patients were randomly assigned to treatment in balanced blocks using a computer-generated randomization schedule; all study personnel were blinded to randomized treatment. Eligible patients were randomly assigned 1:1 to either fulvestrant 500 mg administered as two 5-mL intramuscular injections on days 0, 14, and 28 and every 28 (± 3) days thereafter or fulvestrant 250 mg administered as two 5-mL intramuscular injections (one fulvestrant and one placebo [identical in appearance to study drug]) on days 0, 14 (two placebo injections only), and 28, and every 28 (± 3) days thereafter (9).

Fulvestrant was supplied in the form of a single dose in a prefilled syringe. Each active prefilled syringe contained 250 mg of fulvestrant at a concentration of 50 mg/mL in a volume of 5 mL, designated fulvestrant 5% weight/volume injection. The placebo prefilled syringe was identical to the active prefilled syringe and also had a volume of 5 mL.

Survival analysis

OS was defined as the number of days from randomization to death from any cause. Patients who died after the data cutoff or who were known to be alive after the data cutoff were right-censored at the date of the data cutoff. Patients who were last known to be alive before the data cutoff or who were lost to follow-up before the data cutoff were right-censored at the date they were last known to be alive.

After the initial analysis, patients on fulvestrant 250 mg were permitted to switch to 500 mg before entering the survival follow-up phase. Irrespective of whether they were still receiving randomized treatment, all patients in the follow-up phase continued to have their survival status monitored every 12 ± 2 weeks until cutoff for the final 75% OS analysis (October 31, 2011).

Best Response to First Subsequent Therapy

Details of the first subsequent systemic breast cancer therapy received after discontinuation of randomized treatment, and of the best response (complete response, partial response, stable disease, progressive disease, not evaluable) to this therapy were collected.

Tolerability

SAEs were reported to the Patient Safety Database and collated during the survival follow-up phase for those patients still receiving randomized treatment.

Statistical Analysis

OS was first analyzed in 2009, in parallel with the primary analysis of PFS, after the proportion of reported deaths exceeded 50% of the total number of patients randomized across the two treatment groups. The analysis was performed using an unadjusted log-rank test. An additional exploratory analysis, which used a Cox proportional hazards model adjusting for six predefined covariables (age at baseline, response to last endocrine therapy received before fulvestrant, receptor status at diagnosis, visceral involvement at baseline, last therapy before fulvestrant, and measurable disease at baseline) was also performed to assess the robustness of the unadjusted OS result.

An updated analysis is presented here of more mature survival data, performed after the proportion of reported deaths exceeded 75% of the total number of patients randomized across the two treatment groups. The data were analyzed using log-rank statistics, confirmed by Cox proportional hazards model, and summarized by the method of Kaplan–Meier. *P* values presented are nominal without adjustment for multiplicity, and no alpha was retained for this analysis (the 5% error was used at the initial OS analysis). All statistical tests were two-sided.

For SAEs, summaries and analyses were prepared according to the treatment actually received.

Results

Patients

In total, 736 women (median age = 61.0 years) were randomly assigned between February 2005 and August 2007 from 128 centers in 17 countries (Belgium, Brazil, Chile, Colombia, Czech Republic, Hungary, India, Italy, Malta, Mexico, Poland, Russia, Slovakia, Spain, the United States, Ukraine, and Venezuela) (fulvestrant 500 mg: n = 362; fulvestrant 250 mg: n = 374) (Figure 1). Baseline patient and tumor characteristics, reported previously, were comparable between the treatment groups (9). At the time of the final analysis, 63 patients (8.6%) were lost to follow-up, 16 patients (2.2%) had withdrawn consent, 103 patients (14.0%) were

still being followed up (n = 21 [2.9%] on treatment; n = 82 [11.1%] not on treatment), and 554 patients (75.3%) had died.

For 34 of the 736 patients (4.6%), fulvestrant dose was unblinded after progression to the study drug.

Eight patients (2.1%) crossed over from fulvestrant 250 mg to fulvestrant 500 mg.

Survival Analysis

At the initial data cutoff, 378 of 736 patients (51.4%) had died (n = 175 [48.3%] in the fulvestrant 500 mg group; n = 203 [54.3%] in the fulvestrant 250 mg group) (Table 1). There was a trend for improved OS for patients in the fulvestrant 500 mg group compared with those in the fulvestrant 250 mg group (25.1 months vs 22.8 months, respectively; hazard ratio (HR) = 0.84, 95% confidence interval (CI) = 0.69 to 1.03, $P = .09$ for the unadjusted analysis; HR = 0.81, 95% CI = 0.66 to 1.00, $P = .049$ for the retrospective adjusted analysis) (Table 1; Figure 2A).

At the final survival update, 554 of 736 patients (75.3%) had died (n = 261 [72.1%] in the fulvestrant 500 mg group; n = 293 [78.3%] in the fulvestrant 250 mg group) (Table 1). There was continued separation of the survival curves for fulvestrant 500 mg compared with fulvestrant 250 mg. The median time to death for patients in the fulvestrant 500 mg group vs the fulvestrant 250 mg group was 26.4 months vs 22.3 months, respectively (HR = 0.81, 95% CI = 0.69 to 0.96, nominal $P = .02$ for the unadjusted analysis; HR = 0.79, 95% CI = 0.67 to 0.94, nominal $P = .007$ for the adjusted analysis) (Table 1; Figure 2B).

No statistically significant interaction was observed between the six predefined variables indicated in the Method section and fulvestrant activity (global interaction test $P = .62$), indicating that the overall treatment effect was consistent across the predefined covariables.

Best Response to First Subsequent Therapy

Information on first subsequent therapies was available for 230 (63.5%) and 239 (63.9%) patients treated with fulvestrant 500 mg or 250 mg, respectively. Best response to subsequent therapy is detailed in Table 2. For those randomized patients who had subsequent therapy, response to subsequent therapies was similar between treatment groups: 8.3% vs 8.4% of patients had either complete response or partial response in the fulvestrant 500 mg vs 250 mg groups, respectively; 24.8% and 32.2% of patients had stable disease in the fulvestrant 500 mg vs 250 mg groups, respectively; and 33.5% and 28.5% of patients had progressive disease in the fulvestrant 500 mg vs 250 mg groups, respectively.

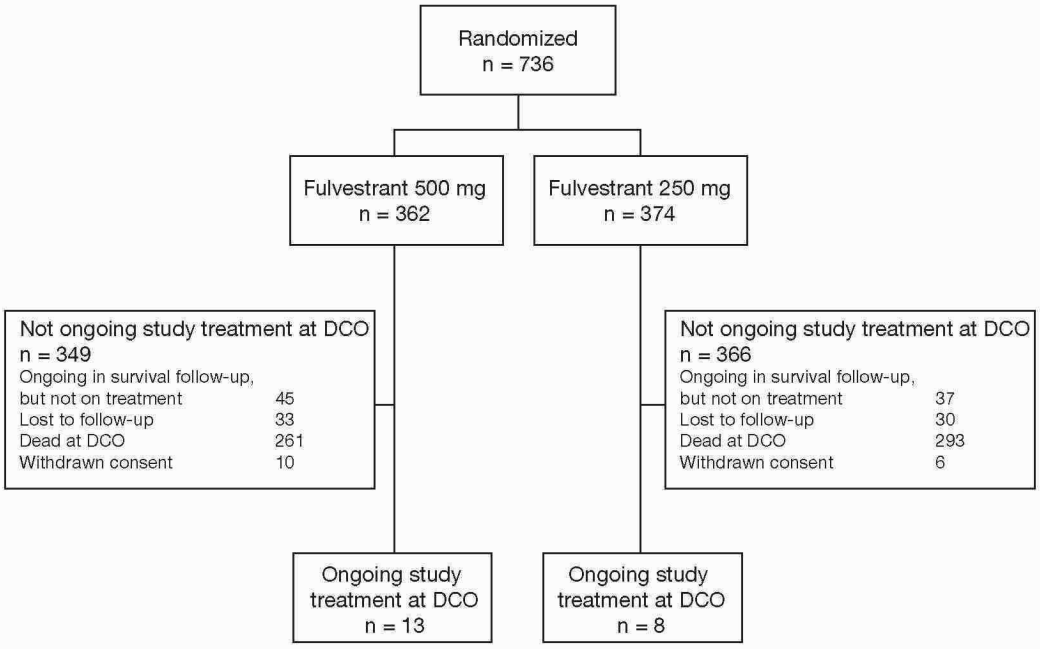

Figure 1. CONSORT diagram. DCO = data cutoff.

Table 1. Summary of overall survival*

Information on overall survival	Initial analysis (50% survival analysis)		Update (75% survival analysis)	
	Fulvestrant 500 mg (n = 362)	Fulvestrant 250 mg (n = 374)	Fulvestrant 500 mg (n = 362)	Fulvestrant 250 mg (n = 374)
No. died (%)	175 (48.3)	203 (54.3)	261 (72.1)	293 (78.3)
Median time to death, mo	25.1	22.8	26.4	22.3
Median time to death, d	764	693	805	679
Time to death, mo: 25% percentile	12.2	11.5	11.7	11.5
Time to death, mo: 75% percentile	NC	41.7	51.1	41.7

* NC = not calculable.

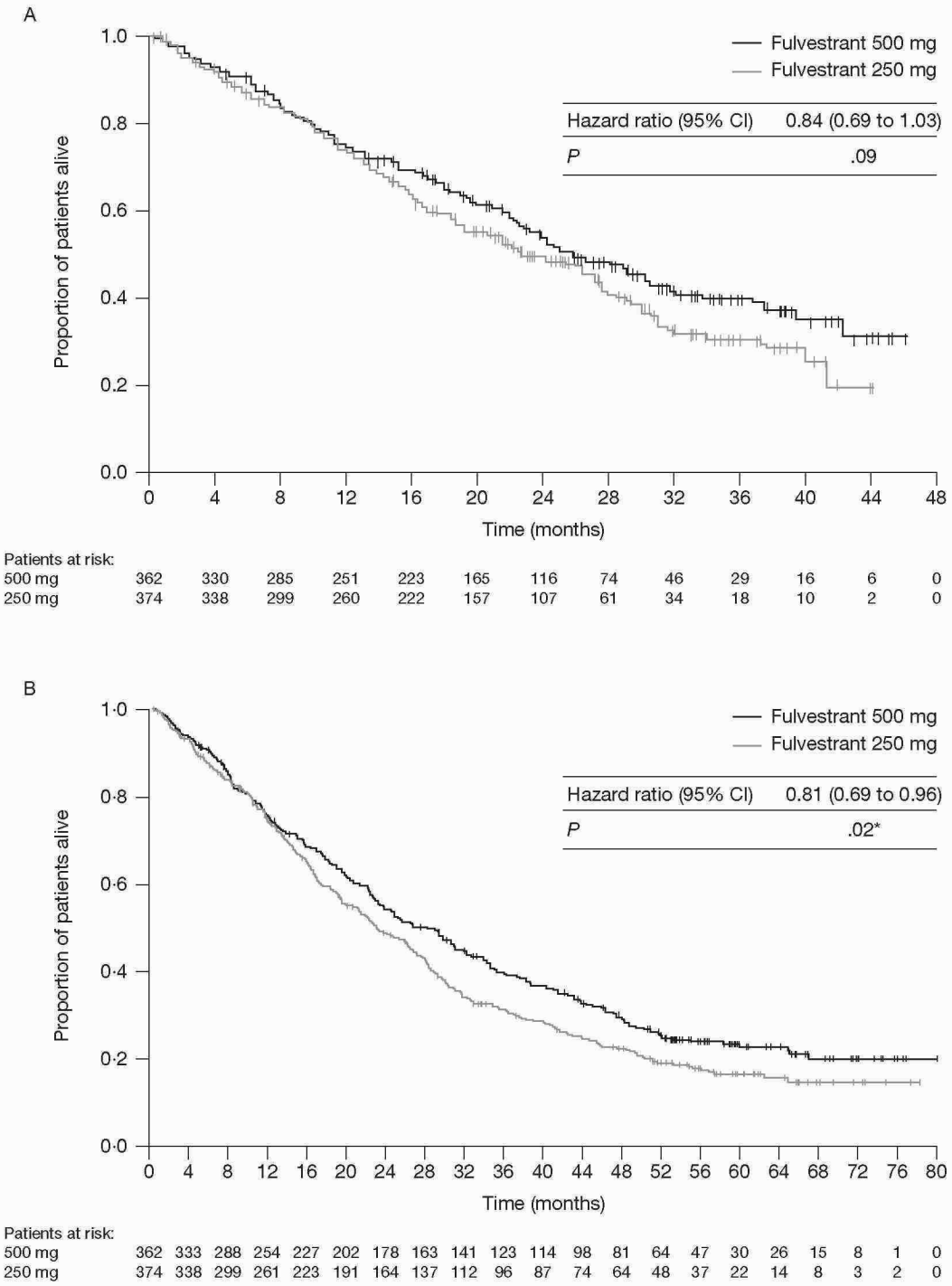

Figure 2. Overall survival from date of randomization. **A**) Overall survival for when 50% of patients had died. **B**) Overall survival for when 75% of patients had died. Analysis by log-rank test. *P* values are two-sided. *No adjustments for multiplicity were made. Tick marks indicate censored observations. CI = confidence interval.

Tolerability

A summary of patients with an SAE during the entire treatment period (main trial plus follow-up phase) is shown in Table 3. During the entire treatment period, a total of 35 (9.7%) and 27 (7.2%) patients had at least one SAE in the fulvestrant 500 mg and fulvestrant 250 mg groups, respectively. SAEs that were causally related to study treatment were reported for eight (2.2%) and four (1.1%) patients, and SAEs with an outcome of death were reported for five (1.4%) and seven (1.9%) patients in the fulvestrant 500 mg and fulvestrant 250 mg groups, respectively, during the entire treatment period. Overall, there were no clinically important differences in the profiles of SAEs between the treatment groups, and no clustering of SAEs could be detected in either treatment group.

Table 2. Best response to subsequent therapy*

Available information on first subsequent therapy	Fulvestrant 500 mg (n = 362) 230	Fulvestrant 250 mg (n = 374) 239
Category of subsequent therapy, No.		
Radiotherapy	8	8
Endocrine therapy	80	74
Chemotherapy	135	142
HER2 directed	0	1
Unknown/other	3	5
Fulvestrant†	4	9
Best response to subsequent therapy, No. (%)		
Complete response	2 (0.9)	0
Partial response	17 (7.4)	20 (8.4)
Stable disease	57 (24.8)	77 (32.2)
Progressive disease	77 (33.5)	68 (28.5)
Not evaluable	77 (33.5)	74 (31.0)

* Subsequent endocrine therapy included: anastrozole, exemestane, letrozole, medroxy progesterone, megestrol acetate, and tamoxifen. HER2 = human epidermal growth factor receptor 2.

† Fulvestrant was either given at a dose of 250 mg or the dose was not specified.

Table 3. Summary of patients experiencing SAEs during the treatment period*

Available information on SAEs	No. of patients (%) Fulvestrant 500 mg (n = 361)	Fulvestrant 250 mg (n = 374)
Patients with at least 1 SAE during the whole trial		
Any SAE	35 (9.7)	27 (7.2)
Any SAE with outcome other than death†	32 (8.9)	22 (5.9)
Any causally related SAE	8 (2.2)	4 (1.1)
SAEs occurring in >1 patient		
Acute myocardial infarction	0 (0)	2 (0.5)
Anemia	3 (0.8)	1 (0.3)
Bronchitis	2 (0.6)	0 (0)
Dyspnea	2 (0.6)	1 (0.3)
Femur fracture	1 (0.3)	2 (0.5)
Hyperglycemia	2 (0.6)	0 (0)
Pneumonia	2 (0.6)	0 (0)
Vomiting	2 (0.6)	1 (0.3)
SAEs with outcome of death, preferred term		
Acute myocardial infarction	0 (0)	2 (0.5)
Acute renal failure	0 (0)	1 (0.3)
Aspiration	0 (0)	1 (0.3)
Cardiopulmonary failure	1 (0.3)	0 (0)
Suicide	0 (0)	1 (0.3)
Death, cause unknown	1 (0.3)	0 (0)
Dyspnea	2 (0.6)	0 (0)
Hypertension	0 (0)	1 (0.3)
Intestinal adenocarcinoma	1 (0.3)	0 (0)
Meningitis	0 (0)	1 (0.3)

* SAEs = serious adverse events.

† All patients experiencing an SAE with nonfatal outcome (regardless of whether they later had a fatal SAE).

Discussion

Preclinical and preliminary clinical data prompted the activation of the CONFIRM trial comparing fulvestrant 500 mg with fulvestrant 250 mg in postmenopausal patients with ER-positive advanced breast cancer (1,5,6,10). The PFS analysis (primary study endpoint of the CONFIRM trial) demonstrated the superiority of 500 mg over 250 mg (9). At the time of the PFS analysis, a first OS analysis was also performed, and approximately 50% of events had been reported. The OS analysis suggested a numerical trend in favor of 500 mg over 250 mg despite the lack of a statistically significant difference (9). This observed numerical trend favoring fulvestrant 500 mg led to a decision by the study Steering Committee to plan for a second OS analysis at 75% maturity.

This article reports the results of the final 75% OS analysis and suggests that fulvestrant 500 mg is superior to fulvestrant 250 mg, with a 19% relative reduction in the risk of death and a 4.1-month increase in median OS. However, a limitation of this study is that the 75% OS analysis is considered exploratory because it was planned after the results of the PFS and 50% OS events analyses were available; accordingly, no alpha was retained for this analysis

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