ORIGINAL REPORT

Results of the CONFIRM Phase III Trial Comparing Fulvestrant 250 mg With Fulvestrant 500 mg in Postmenopausal Women With Estrogen Receptor–Positive Advanced Breast Cancer

Angelo Di Leo, Guy Jerusalem, Lubos Petruzelka, Roberto Torres, Igor N. Bondarenko, Rustem Khasanov, Didier Verhoeven, José L. Pedrini, Iya Smirnova, Mikhail R. Lichinitser, Kelly Pendergrass, Sally Garnett, Justin P.O. Lindemann, Francisco Sapunar, and Miguel Martin

See accompanying editorial 4548

From the Hospital of Prato, Prato, Italy; Centre Hospitalier Universitaire Sart Tilman, Liège; AZ. Klina, Brasschaat, Belgium; Charles University, Prague, Czech Republic; Instituto Nacional del Cáncer, Santiago, Chile; Dnipropetrovsk Municipal Clinical Hospital, Dnipropetrovsk, Ukraine; Republican Clinical Oncological Center, Kazan; Medical Radiological Science Center, Obninsk; Russian Cancer Research Centre, Moscow, Russia; Hospital Nossa Senhora da Conceição, Porto Alegre, Brazil; Kansas City Cancer Center, Kansas City, KS; AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom; and Hospital Universitario Gregorio Maranon, Madrid, Spain.

ABSTRACT

Purpose

We compared fulvestrant 500 mg regimen with the approved dose of fulvestrant 250 mg per month for treatment of postmenopausal women with estrogen receptor–positive advanced breast cancer who experienced progression after prior endocrine therapy.

Patients and Methods

Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) is a double-blind, parallel-group, multicenter, phase III study. Patients were randomly assigned to fulvestrant 500 mg (500 mg intramuscularly [IM] on day 0, then 500 mg IM on days 14 and 28 and every 28 days thereafter) or 250 mg every 28 days. Primary end point was progression-free survival (PFS). Secondary end points included objective response rate, clinical benefit rate (CBR), duration of clinical benefit (DoCB), overall survival (OS), and quality of life (QOL).

Results

PFS was significantly longer for fulvestrant 500 mg (n = 362) than 250 mg (n = 374) (hazard ratio [HR] = 0.80; 95% CI, 0.68 to 0.94; P = .006), corresponding to a 20% reduction in risk of progression. Objective response rate was similar for fulvestrant 500 mg and 250 mg (9.1% v 10.2%, respectively). CBR was 45.6% for fulvestrant 500 mg and 39.6% for fulvestrant 250 mg. DoCB and OS were 16.6 and 25.1 months, respectively, for the 500-mg group, whereas DoCB and OS were 13.9 and 22.8 months, respectively, in the 250-mg group. Fulvestrant 500 mg was well tolerated with no dose-dependent adverse events. QOL was similar for both arms.

Conclusion

Fulvestrant 500 mg was associated with a statistically significant increase in PFS and not associated with increased toxicity, corresponding to a clinically meaningful improvement in benefit versus risk compared with fulvestrant 250 mg.

J Clin Oncol 28:4594-4600. © 2010 by American Society of Clinical Oncology

INTRODUCTION

Fulvestrant is an estrogen receptor (ER) antagonist without known agonistic properties that downregulates cellular levels of ER in a dose-dependent manner.[1-3] Two phase III trials comparing fulvestrant 250 mg with anastrozole in postmenopausal patients with endocrine-sensitive advanced breast cancer pretreated with tamoxifen showed that both treatments have similar efficacy and an acceptable safety profile with a low incidence of withdrawals.[4,5] These results led to the registration of fulvestrant 250 mg as an additional option for the treatment of postmenopausal patients with endocrine-sensitive advanced breast cancer.

Observations from previously reported studies raised the hypothesis that a higher dose of fulvestrant might be associated with increased efficacy. Indeed, results from two preoperative studies, in which patients were exposed short term to different doses of fulvestrant, indicated that ER, progesterone receptor, and the cell proliferation–related antigen Ki-67 were downregulated in a dose-dependent manner after treatment with fulvestrant.[3,6] In addition, a pooled analysis of the two trials comparing fulvestrant 250 mg with anastrozole suggested that a

dose-response effect might exist because the two trials initially included a fulvestrant lower dose arm (125 mg),[4,5,7] which was discontinued after a first interim analysis because it failed to meet the minimum efficacy requirements.[7] More recently, the results of a phase II randomized neoadjuvant study testing two different doses of fulvestrant (ie, 250 v 500 mg) have also suggested that the higher dose might be associated with increased clinical and biologic activity.[8]

Such observations prompted the design of a phase III trial, the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) trial, in which two different doses of fulvestrant were evaluated—the currently approved dose (250 mg every 28 days) and a higher dose regimen that incorporates a day 14 loading element (500 mg on days 0, 14, and 28, and every 28 days thereafter). The present article reports the mature progression-free survival (PFS) results of the CONFIRM trial.

PATIENTS AND METHODS

Eligible patients were postmenopausal and had either locally advanced or metastatic ER-positive breast cancer. No centralized confirmation of ER status was performed. Patients who experienced relapse on adjuvant endocrine therapy or within 1 year from completion of adjuvant endocrine therapy were eligible. For patients who experienced relapse after more than 1 year from completion of adjuvant endocrine therapy or for patients presenting with de novo advanced disease, eligibility required a previous treatment with either an antiestrogen or an aromatase inhibitor as a first-line therapy. Patients with measurable or evaluable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria were eligible.[9] Main exclusion criteria were as follows: presence of extensive liver and/or lung involvement, previous or current history of brain-leptomeningeal metastases, and more than one chemotherapy or endocrine therapy for advanced disease. The study protocol was approved by the institutional review board of each participating institution, and all patients gave written informed consent before study entry.

The trial had a double-blind, placebo-controlled design. Eligible patients were randomly assigned 1:1 to one of the two following treatment arms: fulvestrant 500 mg given as two 5-mL intramuscular (IM) injections, one in each buttock, on days 0, 14, and 28 and every 28 (± 3) days thereafter; or fulvestrant 250 mg given as a two 5-mL IM injections (one fulvestrant injection plus one placebo injection), one in each buttock, on days 0, 14 (two placebo injections only), and 28 and every 28 (± 3) days thereafter. The study treatment had to be administered by a health care professional at the participating institution site. The random assignment was stratified by institution site.

Disease staging at baseline included physical examination, chest x-ray or computed tomography scan, and bone scan or skeletal survey. RECIST tumor assessment was scheduled every 12 (± 2) weeks from the baseline visit until progression. Adverse events were recorded every 4 weeks until 8 weeks from the last injection. Treatment was continued until disease progression unless any of the criteria for early treatment discontinuation, such as patient's withdrawal of consent or severe toxicity, were met first. Subsequent lines of therapy were at the investigator's discretion. No crossover from 250 mg to 500 mg was allowed at the time of disease progression.
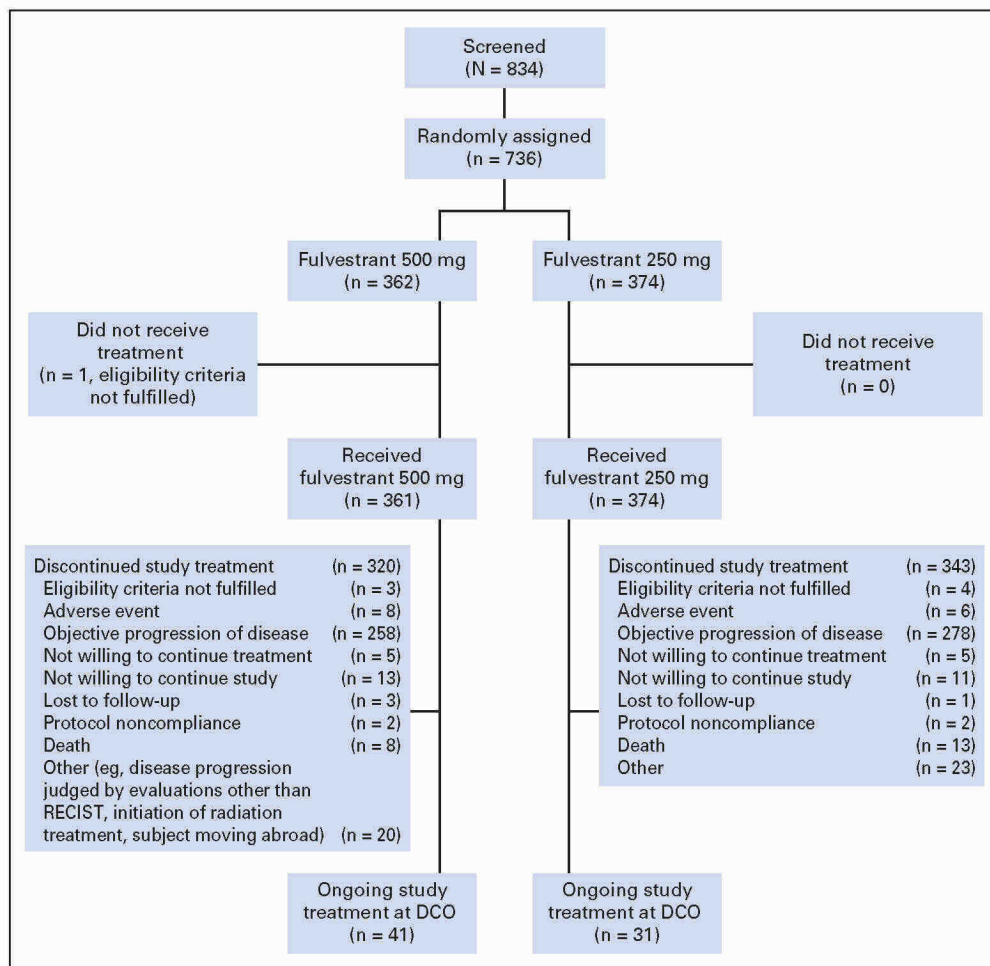

Fig 1. CONSORT diagram. RECIST, Response Evaluation Criteria in Solid Tumors; DCO, data cutoff.

Fig 2. Progression-free survival curves by treatment arm.

Table 2. Objective Response Rates and Clinical Benefit Rates

Response	Fulvestrant 500 mg (n = 362)		Fulvestrant 250 mg (n = 374)	
	No. of Patients	%	No. of Patients	%
Complete response	4	1.1	1	0.3
Partial response	29	8	37	9.9
Objective response*	33	9.1	38	10.2
Stable disease ≥ 24 weeks	132	36.5	110	29.4
Clinical benefit†	165	45.6	148	39.6
Stable disease < 24 weeks	47	13	52	13.9
Progressive disease	140	38.7	167	44.7
Not evaluable	10	2.8	7	1.9

*The complete response plus partial response rate in patients with measurable disease was 13.8% (33 of 240 patients) with fulvestrant 500 mg and 14.6% (38 of 261 patients) with fulvestrant 250 mg.
† Clinical benefit defined as complete response + partial response + stable disease ≥ 24 weeks.

first-line endocrine therapy. Overall, the last endocrine therapy before fulvestrant was an aromatase inhibitor for 42.5% of patients and an antiestrogen for the remaining 57.5% of patients.

Percentages of patients by level of responsiveness to prior endocrine therapy were as follows: 63.3% and 36.7% were considered as responsive and poorly responsive, respectively, in the 500-mg group; and 66.6% and 33.4% of patients were defined as responsive and poorly responsive, respectively, in the 250-mg group.

Efficacy

Figure 2 shows the PFS curves by treatment arm. Fulvestrant 500 mg significantly prolongs PFS over fulvestrant 250 mg (HR = 0.80; 95% CI, 0.68 to 0.94; $P = .006$). This observation is based on a total of 618 progression events, of which 297 (82.0%) were in the 500-mg group and 321 (85.8%) were in the 250-mg group. Median PFS times were 6.5 and 5.5 months in the 500- and 250-mg groups, respectively. At 12 months, 34% and 25% of patients remained alive and progression free on fulvestrant 500 and 250 mg, respectively; these figures were 16% and 11%, respectively, at 24 months.

The PFS analysis adjusted by predefined covariates resulted in an HR of 0.78 (95% CI, 0.67 to 0.92; $P = .003$). Figure 3 shows the PFS forest plot according to the predefined covariates and shows that the treatment effect seems to be consistent across all subgroups.

Objective response and clinical benefit rates are listed in Table 2. Fulvestrant 500 mg was not associated with an increase in objective response and clinical benefit rates (OR for objective response rate = 0.94; 95% CI, 0.57 to 1.55; $P = .795$; OR for clinical benefit rate = 1.28; 95% CI, 0.95 to 1.71; $P = .100$; OR > 1 favors fulvestrant 500 mg).

The time to response analysis reveals that within the first 12 weeks of treatment, seven (18.4%) of the 38 responders had already responded in the 250-mg arm; this percentage was 9.1% in the 500-mg group (three of 33 patients). At week 24, 22 (58%) of the 38 responders and 18 (55%) of the 33 responders had an objective response to fulvestrant 250 and 500 mg, respectively. Median durations of response were 19.4 and 16.4 months for the 500- and
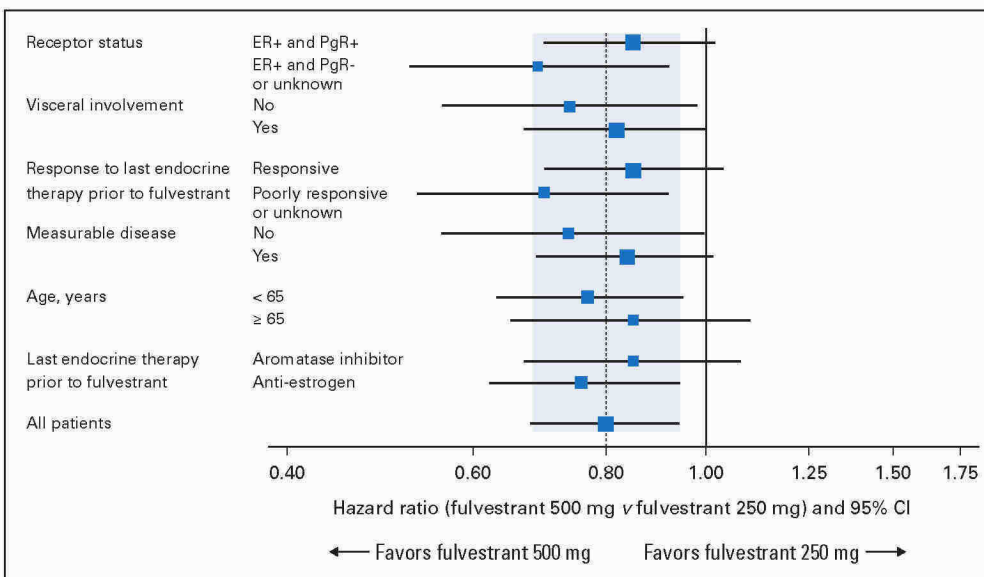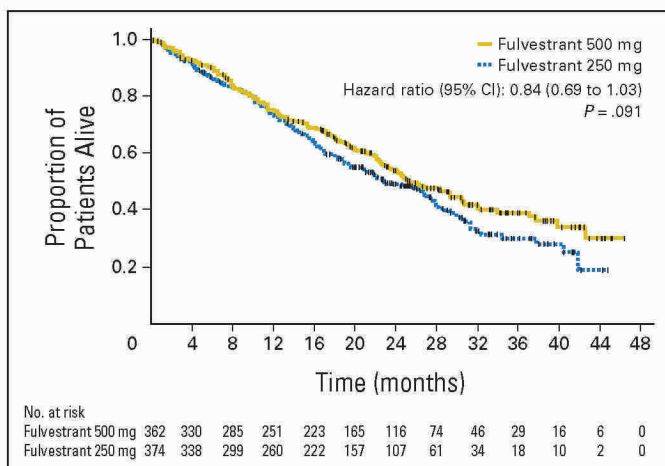

Fig 3. Progression-free survival by predefined covariates. ER, estrogen receptor; PgR, progesterone receptor.

Fig 4. Overall survival curves by treatment arm.

No. at risk												
Fulvestrant 500 mg	362	330	285	251	223	165	116	74	46	29	16	6	0
Fulvestrant 250 mg	374	338	299	260	222	157	107	61	34	18	10	2	0

250-mg groups, respectively, if duration of response was calculated from the date of random assignment. Conversely, if duration of response was calculated from the date on which response was actually detected, median durations were 8.5 and 12 months for the 500- and 250-mg groups, respectively. Median durations of clinical benefit were 16.6 and 13.9 months in the 500- and 250-mg groups, respectively.

Figure 4 shows the OS curves. Median times to death were 25.1 and 22.8 months for fulvestrant 500 mg and 250 mg, respectively (HR = 0.84; 95% CI, 0.69 to 1.03; $P = .091$). A preplanned second survival analysis will be performed when approximately 75% of patients have had an event, and this is expected to occur in 2011.

Safety

Median durations of exposure to fulvestrant were 174 days (range, 10 to 1,441 days) and 145 days (range, 7 to 1,387 days) in the 500- and 250-mg groups, respectively. Table 3 lists the incidence of prespecified adverse events by treatment group. No substantial difference in incidence and severity of adverse events was seen between the two treatment groups. No relevant laboratory abnormalities were observed, and no differences were reported by fulvestrant dose. Serious adverse events reported in ≥ two patients were as follows: bronchitis (n = 2; 0.6%), dyspnea (n = 2; 0.6%), and vomiting (n = 3; 0.8%) in the 500-mg group; no cases were reported in the 250-mg group. Casually related serious adverse events included one patient with interstitial lung disease in the 500-mg group and one patient with blood hypertension in the 250-mg group. The latter was the only instance of a casually related adverse event leading to death from cardiac failure.

QOL

A total of 145 patients completed a baseline FACT-B questionnaire, which represented 82.3% of the 176 patients randomly assigned in the countries that participated in the QOL substudy. Appendix Figure A1 (online only) shows the comparison between the two study arms in terms of QOL evaluated as TOI, which is the main outcome measure of FACT-B. The TOI score is a summary score of the following subscales: physical well-being, functional well-being, and breast cancer subscale. No significant difference was detected between the two study arms.

DISCUSSION

The present randomized trial demonstrates that fulvestrant 500 mg produces a statistically significant and clinically relevant prolongation of PFS over fulvestrant 250 mg. The PFS improvement seems to be the consequence of a modest increase in the rate of disease stabilization and a substantial prolongation in duration of disease stabilization.

OS data seem to favor fulvestrant 500 mg. Interestingly, at the time of this analysis, no crossover from the 250-mg arm to the 500-mg arm has occurred. However, on the basis of data presented here, the independent data monitoring committee has advised to offer crossover to 500 mg for ongoing 250-mg patients. At the time of data cutoff, 31 (8.3%) of 374 patients treated in the 250-mg arm were continuing on treatment, and thus, the overall proportion of crossover patients is expected to be small. Accordingly, it is expected that the low crossover rate will not impact significantly on the planned 75% survival analysis.

The safety and QOL analyses do not raise any concern related to fulvestrant 500 mg compared with 250 mg. However, because of

Table 3. Prespecified Adverse Events by Treatment Arm								
	Fulvestrant 500 mg (n = 361)				Fulvestrant 250 mg (n = 374)			
	Grade 1-4		≥ Grade 3		Grade 1-4		≥ Grade 3	
Adverse Event	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Endometrial dysplasia	0	0	0	0	0	0	0	0
GI disturbances	73	20.2	8	2.2	76	20.3	1	0.3
Hot flashes	30	8.3	0	0	23	6.1	0	0
Injection site reactions	49	13.6	1	0.3	50	13.4	0	0
Ischemic cardiovascular disorders	5	1.4	0	0	7	1.9	3	0.8
Joint disorders	68	18.8	8	2.2	70	18.7	8	2.1
Osteoporosis	1	0.3	0	0	0	0	0	0
Thromboembolic events	3	0.8	2	0.6	6	1.6	4	1.1
Urinary tract infection	8	2.2	1	0.3	8	2.1	1	0.3
Vaginitis	3	0.8	0	0	1	0.3	0	0
Weight gain	1	0.3	0	0	1	0.3	0	0

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.