

## 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 Petruzzelka, 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 doi: 10.1200/JCO.2010.30.6266

### 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. © 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.<sup>1-3</sup> 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.<sup>4,5</sup> 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.<sup>3,6</sup> In addition, a pooled analysis of the two trials comparing fulvestrant 250 mg with anastrozole suggested that a

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 Marañon, Madrid, Spain.

Submitted February 24, 2010; accepted July 9, 2010; published online ahead of print at [www.jco.org](http://www.jco.org) on September 20, 2010.

Written on behalf of the Comparison of Faslodex in Recurrent or Metastatic Breast Cancer (CONFIRM) investigators.

Supported by AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom.

Presented in part at the 32nd Annual San Antonio Breast Cancer Symposium, December 9-13, 2009, San Antonio, TX.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on [JCO.org](http://JCO.org).

Corresponding author: Angelo Di Leo, MD, PhD, "Sandro Pitigliani" Medical Oncology Unit, Hospital of Prato, Piazza dell' Ospedale 2, 59100 Prato, Italy; e-mail: [adileo@usl4.toscana.it](mailto:adileo@usl4.toscana.it).

© 2010 by American Society of Clinical Oncology

0732-183X/10/2899-1/\$20.00

DOI: 10.1200/JCO.2010.28.8415

dose-response effect might exist because the two trials initially included a fulvestrant lower dose arm (125 mg),<sup>4,5,7</sup> which was discontinued after a first interim analysis because it failed to meet the minimum efficacy requirements.<sup>7</sup> 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.<sup>8</sup>

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.

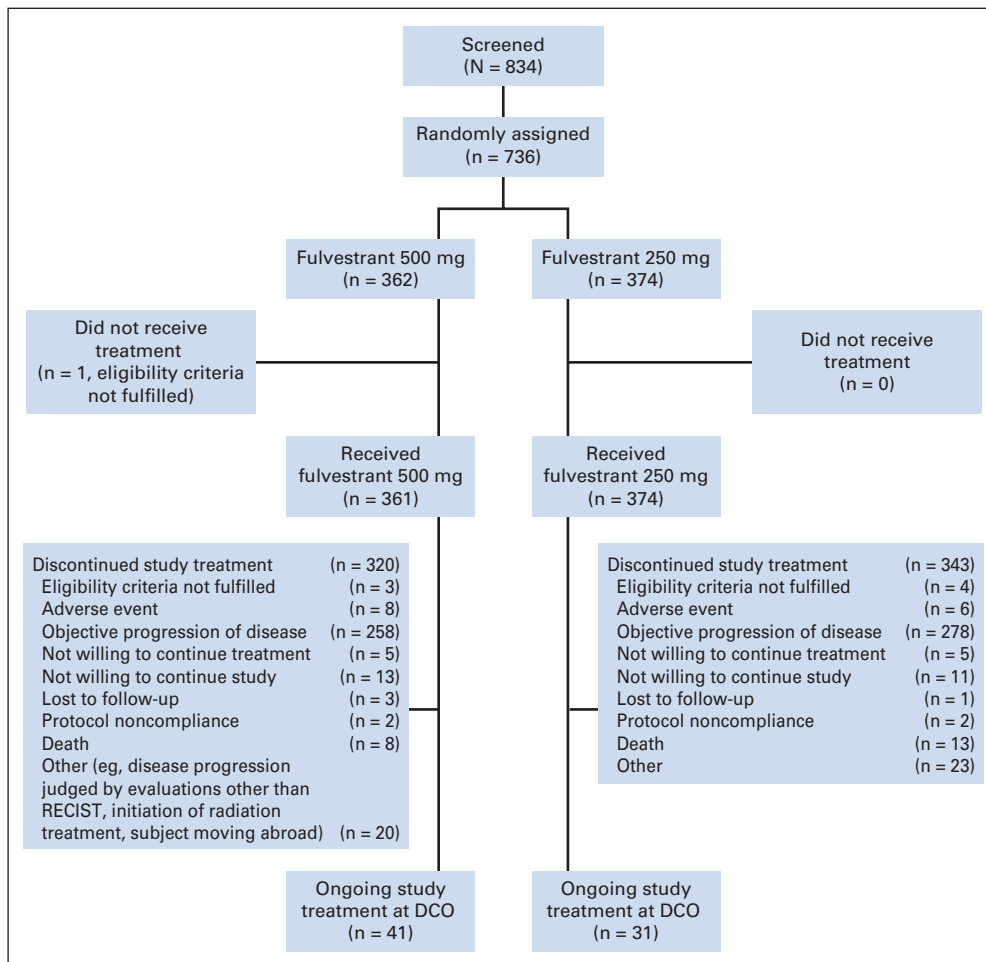
## PATIENTS AND METHODS

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.<sup>9</sup> 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 ( $\pm$  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 ( $\pm$  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 ( $\pm$  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.

The study primary end point was a comparison between the two treatment arms in terms of PFS, which was defined as the time elapsing between the date of random assignment and the date of the earliest evidence of objective disease progression or death from any cause before documented disease progression. Secondary end points were the comparisons between the two treatment arms in terms of objective response rate (complete and partial response), clinical benefit rate (complete response, partial response, and disease stabilization for at least 24 weeks), duration of response and clinical benefit, overall survival (OS), tolerability, and quality of life (QOL).

The sample size calculation was based on the primary variable of PFS and assumed exponential progression times. The sample size was driven by the number of required events. To detect a hazard ratio (HR) of  $\leq 0.8$  (or  $\geq 1.25$ ) for fulvestrant 500 mg compared with 250 mg, at a two-sided significance level of 5%, with 80% power, approximately 632 events were required to have occurred in the study. The median PFS for fulvestrant 250 mg in this patient population was estimated to be 5.5 months,<sup>7</sup> and an HR of 0.8 would equate to a prolongation in median PFS for fulvestrant 500 mg over fulvestrant 250 mg of 1.38 months. If 720 patients were recruited over a period of 36 months, it was anticipated that the required 632 events would be observed approximately 6 months after the end of recruitment.

For the primary end point of PFS, the primary analysis was an unadjusted log-rank test. The treatment effect was estimated using the HR of fulvestrant 500 mg versus fulvestrant 250 mg, together with the corresponding 95% CI and *P* value. Kaplan-Meier plots were presented with estimates of the median for each treatment group. The secondary analysis of PFS was a Cox proportional hazards model, which was adjusted for the following predefined covariates: progesterone receptor status (positive *v* negative or unknown), visceral involvement (no *v* yes), last endocrine therapy before fulvestrant (antiestrogen *v* aromatase inhibitor), age ( $< v \geq 65$  years), measurable disease (no *v* yes), and level of responsiveness to last endocrine therapy before fulvestrant (responsive *v* poorly responsive or unknown). For the latter covariate, a tumor was defined as responsive to last endocrine therapy before fulvestrant if recurrence occurred after 2 or more years on the previous adjuvant endocrine therapy or if complete response, partial response, or disease stabilization for at least 24 weeks was recorded on first-line endocrine therapy for advanced disease. Conversely, a tumor was defined as poorly responsive if recurrence occurred within the first 2 years on adjuvant endocrine therapy or if stable disease for less than 24 weeks or disease progression was the best response to first-line endocrine therapy for advanced disease.

Objective response and clinical benefit rates were summarized and analyzed using a logistic regression model. Results were expressed as the odds ratio (OR) together with the corresponding 95% CI and *P* value. Durations of response and clinical benefit were summarized, and Kaplan-Meier plots were produced with estimates of the median for each treatment group. Duration of response was calculated either from the date of random assignment or from the date of first documented response to the date of progression. Duration of clinical benefit was calculated from the date of random assignment to the date of disease progression. A summary of time to response was also produced. OS was analyzed using an unadjusted log-rank test as described for the PFS analysis. The log-rank test was to be performed when approximately 50% of the randomly assigned patients had died, and this occurred at the time of the present PFS analysis. Incidence of each adverse event by treatment arm was reported. Adverse events were graded according to National Cancer Institute Common Terminology Criteria of Adverse Events (version 3.0).<sup>10</sup> A comparison between the two study arms in the incidence of certain prespecified categories of adverse events was also performed using a two-sided Fisher's exact test at nominal significance of *P* = .05.

The Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire was the instrument used to assess QOL. A subgroup of the trial population completed questionnaires at scheduled clinical visits at baseline and at each 4-week visit for 24 weeks or until progression. The main QOL variable was Trial Outcome Index (TOI).

Adverse events and laboratory abnormalities were summarized by treatment actually received, whereas efficacy and QOL analyses were carried out according to the randomly assigned treatment. The study was sponsored by AstraZeneca (Macclesfield, United Kingdom). Data monitoring was per-

formed by an independent data monitoring committee, which reported to the study sponsor.

## RESULTS

### Patients

A total of 736 patients were recruited from 128 centers across 17 countries (Fig 1). The first patient was randomly assigned on February 8, 2005, and the last patient was randomly assigned on August 31, 2007. The data cutoff date for the primary analysis (February 28, 2009) was chosen based on modeling of the rate of known progression events. At this time, 618 events were recorded.

Table 1 lists main patient and tumor characteristics by treatment group. No relevant imbalances are observed between the two study arms.

Table 1 divides patients by the setting of endocrine therapy before fulvestrant (ie, either adjuvant or for advanced disease). It is worth noting that the most represented subgroups were patients who experienced relapse on adjuvant endocrine therapy and patients who presented with de novo advanced disease and experienced progression on

**Table 1.** Main Patient and Tumor Characteristics

Characteristic	Fulvestrant 500 mg (n = 362)		Fulvestrant 250 mg (n = 374)	
	No. of Patients	%	No. of Patients	%
Median age, years	61		61	
ER positive	362	100	374	100
PgR status				
Positive	241	66.6	266	71.1
Negative	92	25.4	96	25.7
Unknown	29	8	12	3.2
Locally advanced disease	4	1.1	11	2.9
Metastatic disease	358	98.9	363	97.1
Visceral involvement	239	66	232	62
No. of disease sites				
Median	2		2	
Range	1-6		0-7	
Time from diagnosis to random assignment, months				
Median	60.5		59.9	
Range	0.9-338.6		1.9-418.4	
Relapse/progression				
During adjuvant endocrine therapy	175	48.3	169	45.2
0-12 months after completion of adjuvant endocrine therapy	16	4.4	27	7.2
> 12 months after completion of adjuvant endocrine therapy and after progression on first-line endocrine therapy for advanced disease	36	9.9	52	13.9
Patients presenting with de novo advanced disease and experiencing progression on first-line endocrine therapy	130	35.9	125	33.4
Other	5	1.4	1	0.3

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor.

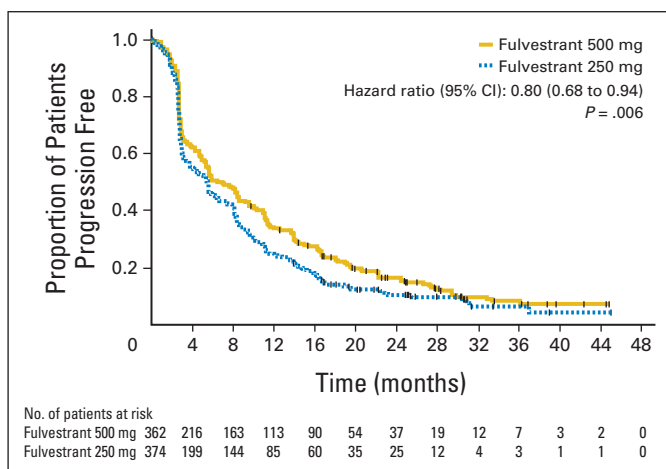


Fig 2. Progression-free survival curves by treatment arm.

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.

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.

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 250-mg groups, respectively.

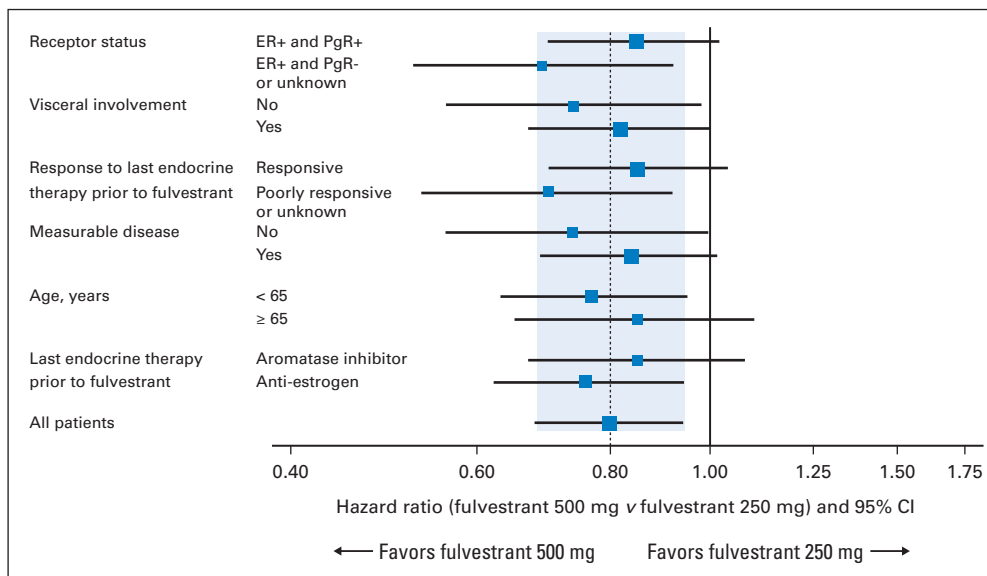


Fig 3. Progression-free survival by predefined covariates. ER, estrogen receptor; PgR, progesterone receptor.

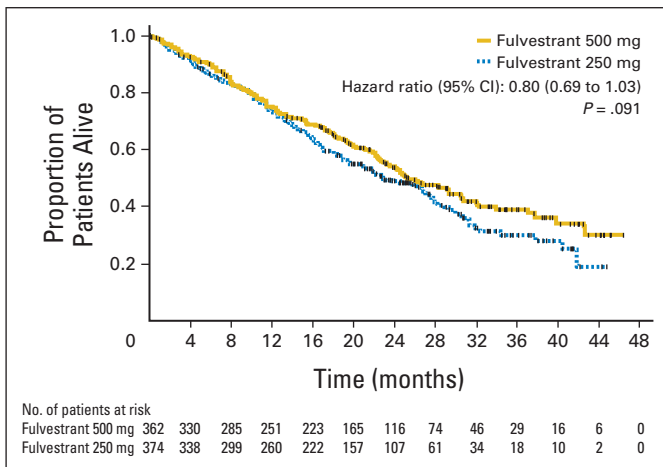


Fig 4. Overall survival curves by treatment arm.

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. Seri-

ous 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

Adverse Event	Fulvestrant 500 mg (n = 361)				Fulvestrant 250 mg (n = 374)			
	Grade 1-4		≥ Grade 3		Grade 1-4		≥ Grade 3	
	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

the inclusion of a placebo injection in the control arm, the present study design is not appropriate to assess any potential increase in the risk of injection site reactions related to the 500-mg dose. Of note, previous investigations into fulvestrant solubility suggest that a more concentrated formulation of fulvestrant (ie, > 250 mg/5 mL) is unlikely to be achieved for slow-release injection (M. Harrison, personal communication).

The results reported in the present article refer to the overall study population. The planned subgroup analysis according to six predefined covariates suggests that the type of treatment effect seems to be consistent across the investigated subgroups (global interaction test,  $P = .801$ ; Fig 3). Nevertheless, it is important to mention that the study was not powered to detect interactions between the investigated covariates and treatment activity. In addition, the study sample size does not allow ruling out the hypothesis that the magnitude of benefit from fulvestrant 500 mg could be modulated by some of the investigated covariates.

The study population, although selected according to well-defined eligibility criteria, remains heterogeneous in terms of some clinical and biologic characteristics. In particular, it is expected that approximately 10% of patients might have tumors carrying activation of the growth factor receptors pathway, and this could ultimately lead to an intrinsic form of resistance to hormone therapy.<sup>11,12</sup> In addition, length of exposure to prior endocrine therapy and interval between date of last hormone therapy treatment and date of fulvestrant start might both contribute to modulate the level of sensitivity to an additional line of endocrine therapy.<sup>12</sup> For instance, patients who were previously exposed long term to hormone therapy (ie, > 2 years) and who received fulvestrant immediately after progression to endocrine therapy could have an acquired form of resistance to hormonal treatment.<sup>12</sup> Preclinical and early clinical data indicate that in this setting, estrogens could paradoxically enhance tumor apoptosis and that, conversely, antihormone agents could lose, at least temporarily, their clinical activity.<sup>13-16</sup> Given these considerations, we hypothesize that the present study population might include a certain proportion of patients with an intrinsic or an acquired form of resistance to hormone therapy. These patients are not expected to derive clinical benefit from fulvestrant at either dose or from other endocrine therapies. In the attempt to corroborate this hypothesis, we are now running a correlative study (ie, Trans-CONFIRM) in which activation of the growth factor receptor pathway at the primary tumor level and duration of exposure to prior hormone therapy will be investigated as potential factors predicting the activity of fulvestrant 500 mg.

In conclusion, the present study has investigated the clinical value of increasing the dose of fulvestrant from 250 to 500 mg in a population of postmenopausal patients with advanced breast cancer with ER-positive tumors previously exposed to at least one endocrine therapy. The results of CONFIRM support previous

data and demonstrate that fulvestrant 500 mg is associated with a statistically significant and clinically relevant increase in PFS, the study primary end point. Increasing fulvestrant dose is not associated with any safety concern. These results indicate that fulvestrant 500 mg IM (on days 0, 14, and 28 and every 28 days thereafter) should replace the currently approved 250-mg schedule in current medical practice.

#### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

*Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.*

**Employment or Leadership Position:** Sally Garnett, AstraZeneca (C); Justin P.O. Lindemann, AstraZeneca (C); Francisco Sapunar, AstraZeneca (C) **Consultant or Advisory Role:** Angelo Di Leo, Pfizer (C), AstraZeneca (C); Miguel Martin, AstraZeneca (C), Pfizer (C) **Stock Ownership:** Sally Garnett, AstraZeneca; Justin P.O. Lindemann, AstraZeneca; Francisco Sapunar, AstraZeneca **Honoraria:** Angelo Di Leo, Pfizer, AstraZeneca; Guy Jerusalem, AstraZeneca **Research Funding:** Angelo Di Leo, Pfizer, AstraZeneca; Guy Jerusalem, AstraZeneca; Kelly Pendergrass, AstraZeneca **Expert Testimony:** Francisco Sapunar, AstraZeneca (C) **Other Remuneration:** None

#### AUTHOR CONTRIBUTIONS

**Conception and design:** Angelo Di Leo, Sally Garnett, Miguel Martin **Financial support:** Justin P.O. Lindemann **Administrative support:** Justin P.O. Lindemann **Provision of study materials or patients:** 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, Justin P.O. Lindemann, Miguel Martin **Collection and assembly of data:** Sally Garnett, Justin P.O. Lindemann **Data analysis and interpretation:** Angelo Di Leo, Guy Jerusalem, Lubos Petruzelka, Sally Garnett, Justin P.O. Lindemann, Francisco Sapunar, Miguel Martin **Manuscript writing:** Angelo Di Leo, Guy Jerusalem, Lubos Petruzelka, Sally Garnett, Justin P.O. Lindemann, Francisco Sapunar, Miguel Martin **Final approval of manuscript:** 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, Miguel Martin

#### REFERENCES

1. Wakeling AE, Dukes M, Bowler J: A potent specific pure antiestrogen with clinical potential. *Cancer Res* 51:3867-3873, 1991
2. Howell A, Osborne CK, Morris C, et al: ICI 182,780 (Faslodex): Development of a novel, "pure" antiestrogen. *Cancer* 89:817-825, 2000
3. Robertson JF, Nicholson RI, Bundred NJ, et al: Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentyl)sulfinyl]-nonyl] estradiol-1,3,5, (10)-triene-3, 17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. *Cancer Res* 61:6739-6746, 2001
4. Howell A, Robertson JF, Quaresma Albano J, et al: Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 20:3396-3403, 2002
5. Osborne CK, Pippin J, Jones SE, et al: Double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant versus anastrozole in postmenopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial. *J Clin Oncol* 20:3386-3395, 2002
6. DeFriend DJ, Howell A, Nicholson RI, et al: Investigation of a new pure antiestrogen (ICI 182780) in women with primary breast cancer. *Cancer Res* 54:408-414, 1994

## Fulvestrant 500 mg in Advanced Breast Cancer

7. Robertson JF, Osborne CK, Howell A, et al: Fulvestrant versus anastrozole for the treatment of advanced breast carcinoma in postmenopausal women: A prospective combined analysis of two multicenter trials. *Cancer* 98:229-238, 2003

8. Kuter I, Hegg R, Singer CF, et al: Fulvestrant 500 mg vs 250 mg: First results from NEWEST, a randomized, phase II neoadjuvant trial in postmenopausal women with locally advanced, estrogen receptor-positive breast cancer. *Breast Cancer Res Treat* 109:589, 2008 (abstr)

9. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 92:205-216, 2000

10. National Cancer Institute: Cancer Therapy Evaluation Program, Common Terminology Criteria

for Adverse Events, Version 3.0. [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

11. Konecny G, Pauletti G, Pegram M, et al: Quantitative association between HER-2/neu and steroid hormone receptors in hormone receptor-positive primary breast cancer. *J Natl Cancer Inst* 95:142-153, 2003

12. Jordan VC: The 38th David A. Karnofsky lecture: The paradoxical actions of estrogen in breast cancer—Survival or death? *J Clin Oncol* 26:3073-3082, 2008

13. Osipo C, Gajdos C, Liu H, et al: Paradoxical action of fulvestrant in estradiol-induced regression of tamoxifen-stimulated breast cancer. *J Natl Cancer Inst* 95:1597-1608, 2003

14. Peethambaram PP, Ingle JN, Suman VJ, et al: Randomized trial of diethylstilbestrol vs. tamoxifen in postmenopausal women with metastatic breast cancer: An updated analysis. *Breast Cancer Res Treat* 54:117-122, 1999

15. Lønning PE, Taylor PD, Anker G, et al: High-dose estrogen treatment in postmenopausal breast cancer patients heavily exposed to endocrine therapy. *Breast Cancer Res Treat* 67:111-116, 2001

16. Ellis MJ, Dehdahti F, Kommareddy A, et al: A randomized phase II trial of low dose (6 mg daily) versus high dose (30 mg daily) estradiol for patients with estrogen receptor positive aromatase inhibitor resistant advanced breast cancer. *Cancer Res* 69:68s, 2009 (suppl; abstr 16)

## Appendix

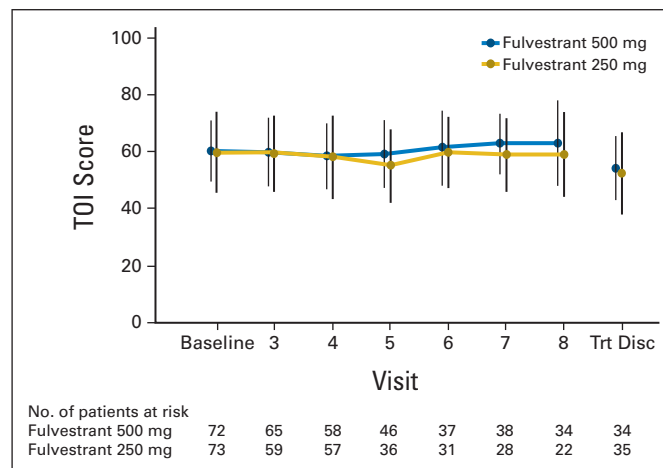


Fig A1. Trial Outcome Index (TOI) by treatment arm. Trt Disc, treatment discontinued.

---

## CORRECTIONS

---

### Author Corrections

The October 20, 2010, article by Di Leo et al, entitled, “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” (J Clin Oncol 28:4594-4600, 2010), contained errors.

In Table 1, in the visceral involvement row, the number of patients in the fulvestrant 500 mg treatment group was given as 239 (66%), whereas it should have been **205 (57%)**. Also, the number of patients in the fulvestrant 250 mg treatment group was given as 232 (62%), whereas it should have been **198 (53%)**.

In Figure 3, the results depicted for no visceral involvement showed an HR of 0.74 (95% CI, 0.56 to 0.98), whereas it should have been an **HR of 0.72 (95% CI, 0.57 to 0.92)**. Also, the results depicted for visceral involvement represent an HR of 0.82 (95% CI, 0.67 to 1.00), whereas it should have been an **HR of 0.86 (95% CI, 0.70 to 1.06)**.

In the Results section, under Efficacy, an HR of 0.78 (95% CI, 0.67 to 0.92;  $P = .003$ ) was given for the PFS analysis in the first sentence of the second paragraph, whereas it should have been an HR of 0.79 (95% CI, 0.68 to 0.93;  $P = .004$ ), as follows: “The PFS analysis adjusted by predefined covariates resulted in an **HR of 0.79 (95% CI, 0.68 to 0.93;  $P = .004$ )**.”

In the Discussion section,  $P = .801$  was given for the global interaction test in the second sentence of the fourth paragraph, whereas it should have been  $P = .796$ , as follows:

“The planned subgroup analysis according to six predefined covariates suggests that the type of treatment effect seems to be consistent across the investigated subgroups (global interaction test,  **$P = .796$** ; Fig 3).”

The authors believe that these errors do not affect the overall results and conclusions of the study, and apologize to the readers for the mistakes.

DOI: 10.1200/JCO.2011.36.8522

---

The February 10, 2011, review article by Burnett, Wetzler, and Löwenberg, entitled, “Therapeutic Advances in Acute Myeloid Leukemia” (J Clin Oncol 29:487-494, 2011), contained an error.

In Table 1, the column heading “GIMEMA/AML 10” should have been labeled “EORTC/GIMEMA.” Also, in the

Abbreviations list, EORTC should have been listed as the European Organisation for Research on Treatment of Cancer.

The authors apologize to the readers for the mistake.

DOI: 10.1200/JCO.2011.36.8530

---

The March 20, 2011, ASCO Special Article by Van Poznak et al, entitled, “American Society of Clinical Oncology Executive Summary of the Clinical Practice Guideline Update on the Role of Bone-Modifying Agents in Metastatic Breast Cancer” (J Clin Oncol 29:1221-1227, 2011) contained an error.

In the Authors’ Disclosure of Potential Conflicts of Interest section, Catherine Van Poznak’s work as a consultant/advisor for Amgen was listed as compensated (C), whereas it should have been listed as uncompensated (U).

The authors apologize to the readers for the mistake.

DOI: 10.1200/JCO.2011.36.8548