

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

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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.

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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.

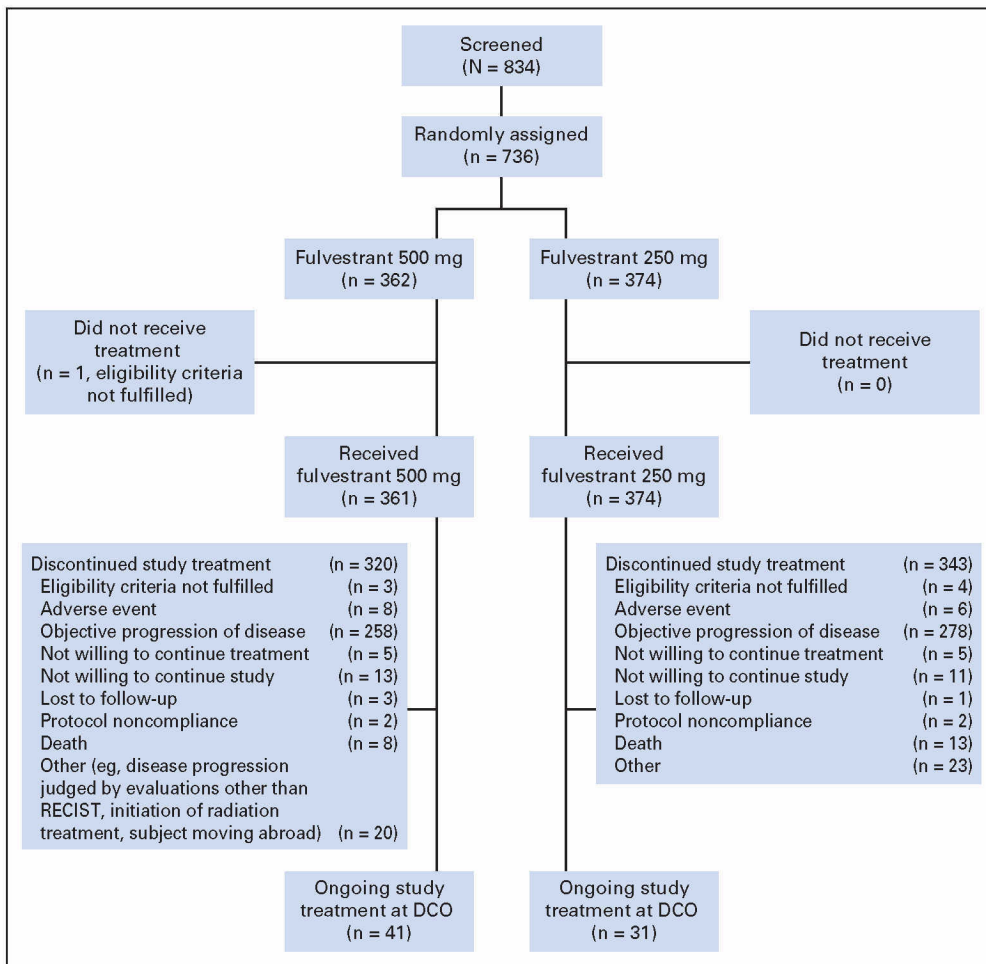


Fig 1. CONSORT diagram. RECIST, Response Evaluation Criteria in Solid Tumors; DCO, data cutoff.

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 ≤ 0.8 (or ≥ 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,⁷ 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).¹⁰ 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.

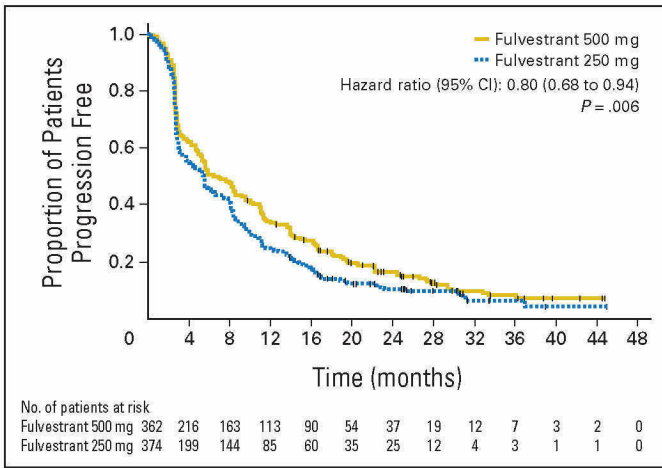


Fig 2. Progression-free survival curves by treatment arm.

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.

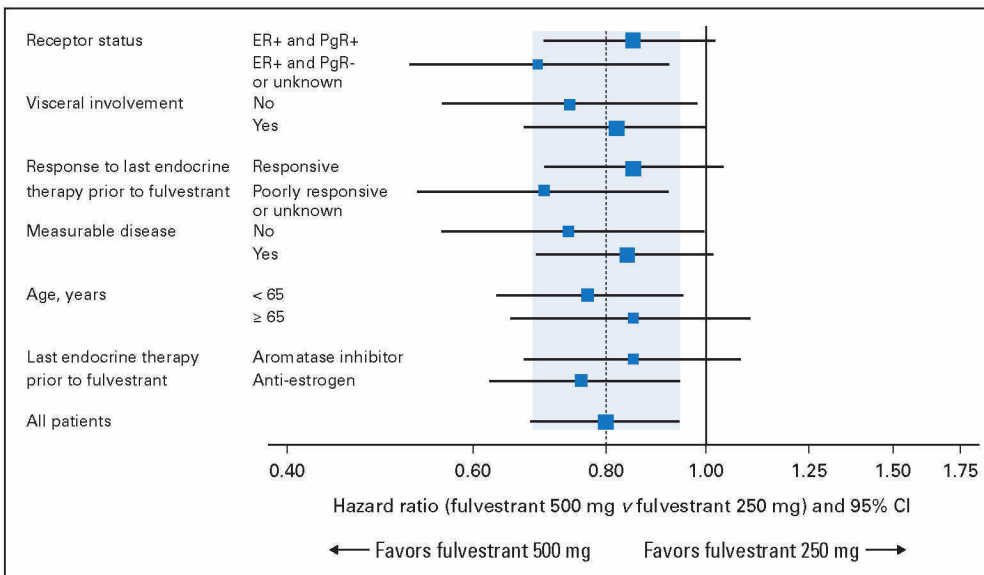


Fig 3. Progression-free survival by predefined covariates. ER, estrogen receptor; PgR, progesterone receptor.

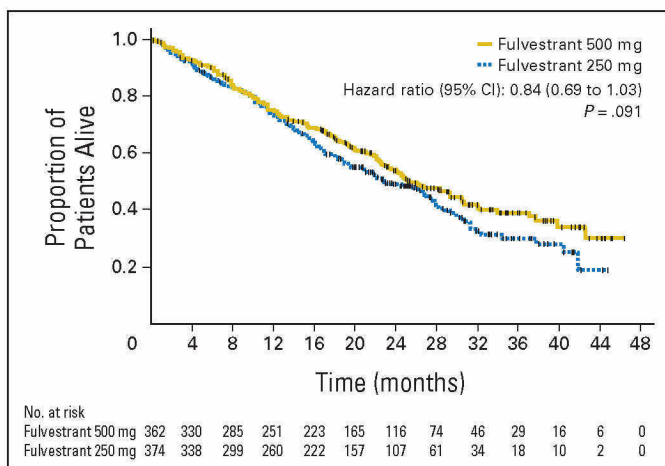


Fig 4. Overall survival curves by treatment arm.

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 \geq 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		\geq Grade 3		Grade 1-4		\geq 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

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