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ORIGINAL REPORT

Double-Blind, Randomized Placebo Controlled Trial of Fulvestrant Compared With Exemestane After Prior Nonsteroidal Aromatase Inhibitor Therapy in Postmenopausal Women With Hormone Receptor–Positive, Advanced Breast Cancer: Results From EFECT

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ABSTRACT

Purpose
The third-generation nonsteroidal aromatase inhibitors (AIs) are increasingly used as adjuvant and first-line advanced therapy for postmenopausal, hormone receptor–positive (HR+) breast cancer. Because many patients subsequently experience progression or relapse, it is important to identify agents with efficacy after AI failure.

Materials and Methods
Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) is a randomized, double-blind, placebo controlled, multicenter phase III trial of fulvestrant versus exemestane in postmenopausal women with HR+ advanced breast cancer (ABC) progressing or recurring after nonsteroidal AI. The primary end point was time to progression (TTP). A fulvestrant loading-dose (LD) regimen was used: 500 mg intramuscularly on day 0, 250 mg on days 14, 28, and 250 mg every 28 days thereafter. Exemestane 25 mg orally was administered once daily.

Results
A total of 693 women were randomly assigned to fulvestrant (n = 351) or exemestane (n = 342). Approximately 60% of patients had received at least two prior endocrine therapies. Median TTP was 3.7 months in both groups (hazard ratio = 0.963; 95% CI, 0.819 to 1.133; $P = .6531$). The overall response rate (7.4% *v* 6.7%; $P = .736$) and clinical benefit rate (32.2% *v* 31.5%; $P = .853$) were similar between fulvestrant and exemestane respectively. Median duration of clinical benefit was 9.3 and 8.3 months, respectively. Both treatments were well tolerated, with no significant differences in the incidence of adverse events or quality of life. Pharmacokinetic data confirm that steady-state was reached within 1 month with the LD schedule of fulvestrant.

Conclusion
Fulvestrant LD and exemestane are equally active and well-tolerated in a meaningful proportion of postmenopausal women with ABC who have experienced progression or recurrence during treatment with a nonsteroidal AI.

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INTRODUCTION

Hormone receptor–positive (HR+) breast cancer is the most common presentation of breast cancer today.[1] In postmenopausal HR+ breast cancer, there are several hormonal therapeutic options available, of which the classes of selective estrogen receptor modulators (SERMs) and aromatase inhibitors (AIs) have been studied extensively and are standard therapeutic options in breast cancer.

The third-generation AIs consists of both nonsteroidal (anastrozole, letrozole) and steroidal (exemestane) inhibitors. The nonsteroidal inhibitors block the peripheral conversion of androgens to estrogens by inhibiting the heme porphyrin portion of aromatase. In contrast, the steroidal AIs act by binding irreversibly to the androgen binding site and are structurally different from the nonsteroidal AIs. As first-line therapy in HR+, postmenopausal advanced breast cancer (ABC),

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the AIs have demonstrated superiority to tamoxifen for response rates and time to progression.[2-4] Furthermore, the AIs, either up front or after tamoxifen, have been clearly established as adjuvant hormonal options in early-stage HR+ postmenopausal breast cancer.[5-10] Unfortunately, the vast majority of patients diagnosed with ABC will eventually progress during treatment with a specific therapy, and a significant proportion of patients with early stage-breast cancers will relapse. Thus, additional therapeutic agents are required to continue to treat the disease at time of progression/relapse.

Fulvestrant is a novel estrogen-receptor (ER) antagonist that, unlike tamoxifen, is devoid of any agonist activity.[11] On binding to the ER, fulvestrant induces a rapid degradation and loss of ER and the progesterone receptor (PgR).[12-13] Several large phase III trials have demonstrated significant activity for fulvestrant in the treatment of HR+ ABC, with similar efficacy to that of anastrozole and tamoxifen.[14-16] Furthermore, activity has been seen in phase II trials of fulvestrant after progression during treatment with a nonsteroidal AI, with clinical benefit rates (CBRs) of 30% to 35%.[17-18]

Exemestane is a steroidal-based AI, with modest androgenic activity.[19] Exemestane has been studied in a phase II trial after documented progression during treatment with a nonsteroidal AI, and showed a 20% clinical benefit rate.[20] Because of the lack of randomized clinical trial data and the prevalence of patients exposed to nonsteroidal AIs, the Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) was undertaken to address this specific question of which hormonal agent to consider first after progression during treatment with a nonsteroidal AI.

MATERIALS AND METHODS

Study Design

EFECT is a randomized, double blind, double-dummy, phase III international trial designed to compare the efficacy and tolerability of a loading-dose (LD) schedule of fulvestrant to exemestane in postmenopausal women with HR+ ABC with disease progression after prior nonsteroidal AI therapy.

Patient Population

All patients were postmenopausal women with incurable locally advanced or metastatic breast cancer whose disease had relapsed during treatment with (or within 6 months of discontinuation of) an adjuvant nonsteroidal AI, or whose advanced disease progressed during treatment with a nonsteroidal AI. Patients were categorized as AI sensitive if the investigator determined that the patient had a complete response (CR), partial response (PR), or stable disease (SD) for at least 6 months during treatment with the AI for ABC. All other patients, including all those who received the AI as adjuvant therapy, were defined as AI resistant.

Inclusion onto the trial required women to be postmenopausal ($\geq$ 60 years old, or age $\geq$ 45 years with amenorrhea for $>$ 12 months or follicle stimulating hormone levels within postmenopausal range, or prior bilateral oophorectomy). Other inclusion criteria included HR+ (ER and/or PgR) disease as determined locally, WHO performance status of 0 to 2, life expectancy of at least 3 months and the presence of at least one measurable or assessable (nonmeasurable) lesion. Initially, the protocol required that all patients have at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST) criteria, but subsequently the protocol was amended to include patients with bone only (lytic or mixed) metastatic lesions. Up to one prior chemotherapy regimen for the treatment of ABC was allowed.

Exclusion criteria included life threatening metastatic visceral disease, brain or leptomeningeal metastases, prior exposure to either fulvestrant or exemestane, extensive radiation or cytotoxic therapy within the last 4 weeks, or a history of bleeding diathesis or need for long-term anticoagulation.

All women provided written informed consent before registration on trial. The study was conducted in accordance with the ethical principles that originated in the Declaration of Helsinki and with local Research Ethics Board approval at each participating center.

Trial Treatments

Fulvestrant 250 mg/5 mL (×2) as an intramuscular injection or a matching 5 mL (×2) oily excipient placebo was injected into each buttock (500 mg or matching placebo) on day 1, followed by a single injection of 250 mg fulvestrant/placebo at day 14 and again on day 28. Treatment after day 28 was every 28 days (± 3 days) thereafter. Exemestane 25 mg and a matching placebo were to be taken orally once daily.

Patients continued treatment until objective disease progression or other events that required withdrawal. There was no built in crossover design in this trial. Thereafter, patients were followed up until death. Patients who withdrew from trial treatment before progression were followed up for response until progression and death.

All patients were seen by a physician monthly until month 6, and every 3 months thereafter. Tumor assessment was performed every 8 weeks from baseline until month 6, and then every 3 months until disease progression.

In a subset of 60 patients (30 in each treatment group) pharmacokinetic samples were collected at specified time intervals to confirm whether the LD regimen would achieve steady-state earlier than that seen previously with a dose of fulvestrant 250 mg every 28 days.

Statistical Analysis

The primary end point of the study was time to disease progression (TTP). Secondary end points included objective response (OR) rate, CBR, duration of response, time to response, overall survival, and tolerability. The trial was designed to detect superiority of fulvestrant compared with exemestane in terms of TTP. The final analysis was scheduled to take place when 580 progression events (ie, objective disease progression or death) had occurred across both treatment groups. This would provide 90% power to detect a hazard ratio of 1.31 or greater, or of 0.76 or less for fulvestrant treatment compared with exemestane treatment, at a two-sided significance level of 5%. To achieve the required number of events, it was planned to recruit 660 patients (330 in each treatment group). Data for the efficacy parameters were analyzed and summarized on an intention-to-treat basis.

TTP

TTP was defined as the number of days from the date of random assignment until the date of objective disease progression, as per RECIST criteria. If the patient died without documented disease progression, and the date of death was no more than 6 months from the last disease assessment per RECIST, then death was regarded as a progression event. For patients who had not experienced disease progression at the time of data cutoff, data were right censored to the date of the last RECIST assessment.

The primary analysis for TTP was the unstratified log-rank test. The secondary analysis used the Cox proportional hazards regression model and included the following six baseline covariates: age ($<$ 65 *v* $\geq$ 65 years), number of prior hormonal therapies (1 *v* $\geq$ 2), receptor status (both ER+ and PgR+ *v* only one receptor positive), visceral involvement (yes *v* no), presence of measurable disease compared with nonmeasurable disease, and AI sensitive versus AI resistant. The treatment effect was estimated using the hazard ratio of fulvestrant to exemestane, together with the 95% CI and *P* value. A global interaction test using a 1% significance level was performed to determine whether the overall treatment benefit was consistent across each of the six covariates. TTP was also summarized using Kaplan-Meier curves for each treatment group and the median TTP was calculated.

Overall Survival

Time to death was to be analyzed when more than 50% of the patients had died across both treatment groups. At the time of data analysis, only 34% of patients had died, and therefore no formal statistical analyses were conducted.

Best OR and CBR

An OR was defined as a patient having a best overall response of either CR or PR with confirmation criteria as per RECIST. A patient with clinical

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benefit (CB) was defined as a patient having a best overall response of a CR, PR, or SD for at least 24 weeks. SD was defined, as per RECIST criteria, as neither achieving a PR nor progressive disease at week 24 or later.

Duration of Response

Duration of response (DOR) was evaluated only for patients who had an OR, and was defined as the number of days from date of random assignment until the day on which disease progression or death resulting from any cause was first observed.

Quality of Life

Quality of life (QOL) was assessed using the Functional Assessment of Cancer Therapy–Endocrine Symptom (FACT-ES) instrument. The analysis was undertaken using both the FACT-ES and Trial Outcome Index (TOI). The difference between the two treatment groups in FACT-ES and TOI over time was compared using a generalized linear mixed model, with the Restricted Maximum Likelihood option, including the same six covariates as for TTP.

Tolerability

All safety data were listed and summarized according to the treatment received. Adverse events (AEs) were presented using MedDRA terminology. Eight AE categories considered relevant to endocrine therapy were predefined for statistical analysis. The analysis of the predefined AEs was performed using a two-sided Fisher's exact test at the 5% significance level.

RESULTS

Patients

A total of 693 women across 138 centers worldwide were randomly assigned to either fulvestrant (n = 351) or exemestane (n = 342) from August 2003 to November 2005. The accountability of all patients randomly assigned is seen in Figure A1 (online only). Baseline characteristics between the two randomly assigned treatments are outlined in Table 1. Overall, the groups were well balanced, except that the fulvestrant cohort had a slightly greater number of women with ER+ and PgR+ tumors (67.5%) versus the exemestane cohort (56.4%). Approximately 60% of participants had two or more prior lines of hormonal therapy. Approximately 60% of patients in both groups had either a response (CR or PR) or SD lasting at least 6 months during treatment with the prior nonsteroidal AI for ABC (termed AI sensitive) as determined by the individual investigator. Only 10% of women enrolled received their previous AI as adjuvant therapy. The median follow-up for all patients alive is approximately 13 months.

Efficacy

The primary end point of this study was TTP. At the time of analysis, 82.1% (n = 288) of the fulvestrant group and 87.4% (n = 299) of the exemestane group had experienced a defined progression event. The median time to progression (Fig 1) in both groups was 3.7 months (P = .65) with a hazard ratio of 0.93 (95% CI, 0.819 to 1.133). The adjusted hazard ratio for the specified covariates was 0.968 (P = .70) with the 95% CI at 0.822 to 1.141. In an investigation of the consistency of treatment effect across the predefined covariates, there were no statistically significant differences (Fig 2).

OR Rate and CBR

A total of 540 patients (270 in each arm) had measurable disease by RECIST criteria at trial entry. Overall, 20 patients in the fulvestrant arm (7.4%) and 18 patients in the exemestane arm (6.7%) had a documented response (odds ratio = 1.12; 95% CI, 0.578 to 2.186; P = .736). The CBR was 32.2% and 31.5% in the fulvestrant and exemestane arms, respectively (odds ratio = 1.03; 95% CI, 0.72 to 1.487; P = .853). Of note, in the cohort of patients with visceral involvement, the CBR was 29% and 27% in the fulvestrant and exemestane arms, respectively.

The median DOR, as measured from the date of random assignment, was 13.5 months in the fulvestrant group and 9.8 months in the exemestane group (Fig 3); median DOR as measured from the date of first response was 7.5 months for fulvestrant compared with 5.5 months for exemestane.

Pharmacokinetics

The pharmacokinetic (PK) substudy results mirrored those from modeling studies and demonstrated a much faster time to steady-state levels with the LD schedule of fulvestrant, compared to prior PK studies of the 250 mg monthly dose. Median time to steady state was achieved within 28 days with the LD regimen, compared with 3 to 6 months with the 250-mg monthly dose[22] (Fig 4).

Tolerability

Both fulvestrant and exemestane were well tolerated in this study (Table 2), with only 2% of fulvestrant-treated patients and 2.6% of exemestane-treated patients withdrawing because of an adverse event (AE). Drug-related serious AEs (SAEs) were rare, occurring in 1.1% and 0.6% of each arm, respectively. No patient died as a result of a drug-related AE. The incidence of venous thromboembolic events in the fulvestrant and exemestane arms was 1.1% and 0.9%, respectively.

QOL

QOL was measured with two instruments in this study, the FACT-ES and TOI. A graph of the mean TOI over time is shown in Figure A2 (online only). The mean difference across both instruments was not significant, demonstrating that QOL was not statistically different between either treatment arms.

DISCUSSION

EFECT is not only one of the largest published trials to date comparing hormonal therapies in HR+ ABC, but also one of the first to specifically address the optimal agent to use in sequence immediately after progression of a nonsteroidal AI. EFECT confirmed efficacy for both fulvestrant and exemestane in this setting, with clinical benefit rates of approximately 32% and a median TTP of 3.7 months for both agents. The observed durations of response with fulvestrant and exemestane (13.5 *v* 9.8 months, respectively) and durations of clinical benefit (9.3 *v* 8.3 months, respectively), are encouraging for a population of patients with relapsed disease after AI treatment. Furthermore, results from EFECT support the concept that patients achieving SD lasting at least 24 weeks have similar outcomes compared with patients obtaining a response (Fig A3, online only), even in this previously hormonally treated population.

It is interesting, that for more than 60% of women in EFECT, the treating oncologist identified the patient as AI sensitive, but this was neither confirmed centrally or by RECIST criteria. Yet by 6 months, approximately 70% of trial subjects had experienced disease progression. This indicates that approximately two thirds of patients did not benefit from either hormonal agent, implying that the majority of

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Table 1. Baseline Patient and Disease Characteristics

Characteristic	Fulvestrant (n = 351)		Exemestane (n = 342)	
	No.	%	No.	%
Age, years				
Median	63		63	
Range	38-88		32-91	
Age group, years				
< 65 (adult)	189	53.8	194	56.7
≥ 65 (elderly)	162	46.2	148	43.3
Prior treatments				
Adjuvant endocrine therapy*	217	61.8	199	58.2
Endocrine therapy for advanced disease†	313	89.2	294	86.0
1 prior endocrine therapy	145	41.3	147	43.0
> 1 prior endocrine therapy	206	58.7	195	57.0
Adjuvant chemotherapy	147	41.9	168	49.1
Chemotherapy for advanced disease	87	24.8	74	21.6
Adjuvant radiotherapy	190	54.1	171	50.0
Radiotherapy for advanced disease	129	36.8	142	41.5
Other breast cancer treatment	35	10.0	29	8.5
AI-sensitive disease	224	63.8	210	61.4
AI-resistant disease	127	36.2	132	38.6
Disease stage‡				
Locally advanced	8	2.3	10	2.9
Metastatic	342	97.4	332	97.1
Sites of metastases§				
Bone	236	67.2	227	66.4
Lung	121	34.5	124	36.3
Liver	109	31.1	110	32.2
Lymph nodes	104	29.6	117	34.2
Skin/soft tissue	71	20.2	58	17.0
Other	48	13.7	56	16.4
Visceral involvement				
Yes	197	56.1	198	57.9
No	154	43.9	144	42.1
Hormone receptor status				
ER+ and/or PgR+	345	98.3	336	98.2
ER+ and PgR+	237	67.5	193	56.4
Other‖	6	1.7	6	1.8
WHO performance status				
0 (normal activity)	194	55.3	181	52.9
1 (restricted activity)	133	37.9	149	43.6
2 (in bed ≥ 50% of the time)	24	6.8	12	3.5
Measurable disease				
Yes	270	76.9	270	78.9
No	81	23.1	72	21.1

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; AI, aromatase inhibitor.
*Thirty-eight patients (10.8%) in the fulvestrant group and 48 (14.0%) patients in the exemestane group received their last non-steroidal AI therapy as adjuvant therapy.
†Three hundred ten patients (88.3%) in the fulvestrant group and 293 (85.7%) in the exemestane group received their last non-steroidal AI therapy for advanced disease.
‡Disease stage was unknown in one patient in the fulvestrant group (patients subsequently classed as a violator).
§Patients could have > 1 site of metastases.
‖One patient in the fulvestrant group and five patients in the exemestane group had no evidence of meeting the criterion for ER of PgR positivity at baseline and so were classed as violators. The remaining five patients in the fulvestrant group and one patient in the exemestane group did not meet this criterion at baseline but met it previously and so weren't considered violators.

patients enrolled on EFECT had hormone-insensitive disease. In addition, in close to 60% of women, the study hormonal agent was administered as third-line or greater therapy. All of these factors could have contributed to a less-than-optimal clinical efficacy than had been hoped for, and may have undermined the power of the study. Indeed, in a retrospective analysis looking at TTP in patients who received fulvestrant or exemestane as second-line treatment and were deemed to be sensitive to the prior nonsteroidal AI, the curves do appear to separate in favor of fulvestrant (hazard ratio = 0.73; 99.8% CI, 0.45 to 1.19; Fig A4, online only). However, the number of patients contributing to this analysis is small (n = 190), and the results are nonsignificant as well as being retrospectively derived.

When used earlier in the hormonal treatment sequence of ER+ ABC, fulvestrant has demonstrated significantly better clinical outcomes than those seen here. As first line therapy fulvestrant was shown to be similar to tamoxifen, with a clinical benefit rate of 57% and a

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Table 2. Most Commonly Occurring Treatment-Related Adverse Events (> 2% incidence in either treatment group)

Adverse Event	Fulvestrant (n = 351) No.	Fulvestrant (n = 351) %	Exemestane (n = 340) No.	Exemestane (n = 340) %
Injection-site pain	33	9.4	28	8.2
Hot flashes	31	8.8	39	11.5
Nausea	24	6.8	27	7.9
Fatigue	22	6.3	34	10.0
Myalgia	14	4.0	14	4.1
Arthralgia	13	3.7	19	5.6
Diarrhea	12	3.4	10	2.9
Asthenia	11	3.1	7	2.1
Injection-site reaction	8	2.3	7	2.1
Alopecia	8	2.3	5	1.5
Headache	7	2.0	10	2.9
Anorexia	7	2.0	7	2.1
Dyspepsia	3	0.9	7	2.1
Pain in extremity	1	0.3	8	2.4

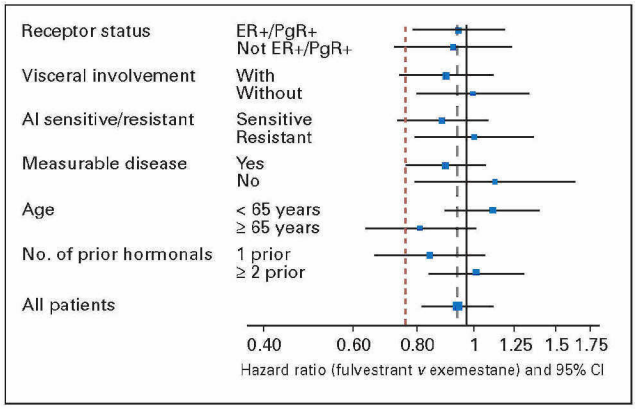

Fig 2. Forest plot of effect of predefined covariates on time to progression. ER, estrogen receptor; PgR, progesterone receptor.

median TTP of 8.2 months.[16] In a combined analysis of two multicenter trials as either first- or second-line therapy in ABC compared with anastrozole, fulvestrant demonstrated a clinical benefit rate of 43.5% and a median TTP of 5.5 months.[21] Interestingly in a relatively small phase II trial of fulvestrant administered immediately after progression during treatment with an AI, in the subset of patients whose only prior hormonal therapy was an AI, the clinical benefit rate was 52.4% (95% CI, 32.8% to 71.4%).[17] Of note, in EFECT, there was no difference in either CBR or median TTP between the predefined subgroup of patients exposed to only one prior hormonal agent or two or more prior hormonal agents.

As a pure ER antagonist, fulvestrant is in a distinct class of its own in regard to its mechanism of action. When fulvestrant binds to the ER, it results in reduced nuclear uptake of the ER-fulvestrant complex, prevention of the ER binding to the estrogen-responsive genes, and, ultimately, downregulation of ER levels.[23-27] Given a distinctly different mechanism of action, it was rational to assume that a substantial degree of clinical activity would be seen with fulvestrant in this setting. The clinical activity seen with fulvestrant in EFECT is similar to those in a previously published experience.[18,28-30]

What perhaps was surprising from this study was the clinical activity seen with exemestane in this setting: The CBR of 31.5% was higher than the 20% CBR reported in a phase II trial, even though the median TTP was similar.[20] EFECT reinforces the notion of incomplete resistance between the nonsteroidal and steroidal AIs. This incomplete cross-resistance is likely not a result of differences in the degree of aromatase inhibition between the AIs.[31-32] It may be caused by the androgenic effects of exemestane.[19-20]

Some questions still remain unanswered today in regard to the optimal use of fulvestrant in the treatment of breast cancer. A higher dose is currently being investigated in several trials. The combination

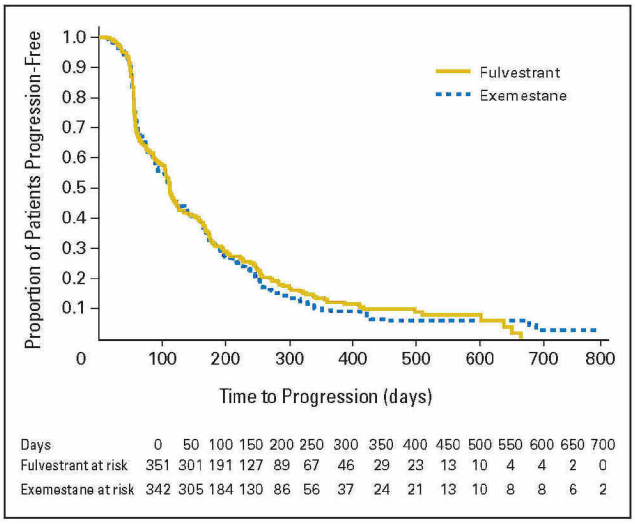

Fig 1. Kaplan-Meier estimates for time to progression (TTP). Estimated median TTP for patients receiving fulvestrant was 3.7 months, compared with 3.7 months for patients receiving exemestane (hazard ratio = 0.963; 95% CI, 0.819 to 1.133; $P = .6531$).

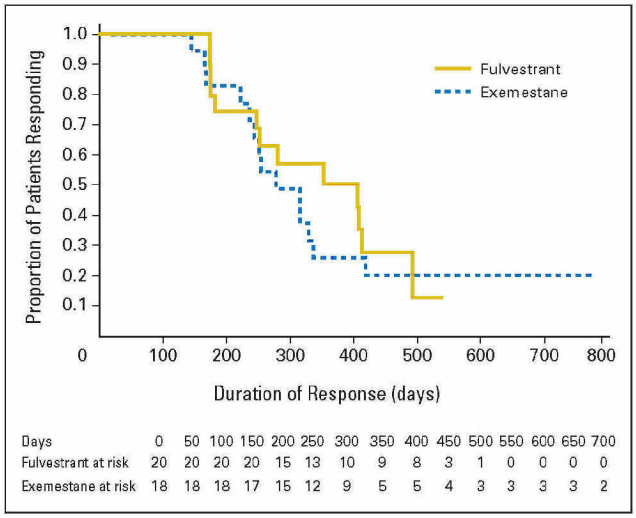

Fig 3. Kaplan-Meier estimates for duration of response (DOR; from random assignment). Estimated median DOR for patients receiving fulvestrant was 13.5 months, compared with 9.8 months for patients receiving exemestane.

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