

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 EFACT

Stephen Chia, William Gradishar, Louis Mauriac, Jose Bines, Frederic Amant, Miriam Federico, Luis Fein, Gilles Romieu, Aman Buzdar, John F.R. Robertson, Adam Brufsky, Kurt Possinger, Pamela Rennie, Francisco Sapunar, Elizabeth Lowe, and Martine Piccart

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 (EFACT) 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.

J Clin Oncol 26:1664-1670. © 2008 by American Society of Clinical Oncology

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),

From the Division of Medical Oncology, British Columbia Cancer Agency, University of British Columbia, Vancouver, British Columbia, Canada; Division of Hematology and Medical Oncology, Feinberg School of Medicine, Northwestern University, Chicago, IL; Department of Medical Oncology, Institut Bergonié, Bordeaux; Department of Medical Oncology, CRLC Val d'Aurelle-Paul Lamarque, Montpellier, France; Medical Oncology, Instituto Nacional de Cancer, Rio de Janeiro; Departamento de Radiologia, Faculdade de Medicina da USP, University of São Paulo, São Paulo, Brazil; Division of Gynecologic Oncology, Department of Obstetrics and Gynecology, University Hospitals Leuven, Leuven; Medicine Department, Jules Bordet Institute, Brussels, Belgium; Investigación Clínica, Centro Oncológico de Rosario, Rosario, Argentina; The M.D. Anderson Cancer Center, University of Texas, Houston, TX; Professorial Unit of Surgery, Nottingham City Hospital, Nottingham; Clinical Development, AstraZeneca Pharmaceuticals, Macclesfield, Cheshire, United Kingdom; Division of Hematology/Oncology, University of Pittsburgh School of Medicine, Pittsburgh, PA; Department of Oncology and Haematology, Charité Campus Mitte, Universitätsmedizin, Berlin, Germany; and Clinical Development, AstraZeneca Pharmaceuticals, Wilmington, DE.

Submitted July 26, 2007; accepted December 5, 2007; published online ahead of print at www.jco.org on March 3, 2008.

Presented in part at the 29th Annual San Antonio Breast Cancer Symposium December 14-17, 2006, San Antonio, Texas.

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

Corresponding author: Stephen Chia, MD, Division of Medical Oncology, British Columbia Cancer Agency, University of British Columbia, 600 West 10th Avenue, Vancouver, B.C. Canada, V5Z 4E6; e-mail: schia@bccancer.bc.ca.

© 2008 by American Society of Clinical Oncology

0732-183X/08/2610-1664/\$20.00

DOI: 10.1200/JCO.2007.13.5822

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 (EFFECT) 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

EFFECT 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 (≥ 60 years old, or age ≥ 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 ($\times 2$) as an intramuscular injection or a matching 5 mL ($\times 2$) 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 ≥ 65 years), number of prior hormonal therapies (1 v ≥ 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

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 dose²² (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

EFFECT 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. EFFECT 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 EFFECT 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 EFFECT, 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

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 or 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 EFFECT 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

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

Adverse Event	Fulvestrant (n = 351)		Exemestane (n = 340)	
	No.	%	No.	%
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

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 EFACT, 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

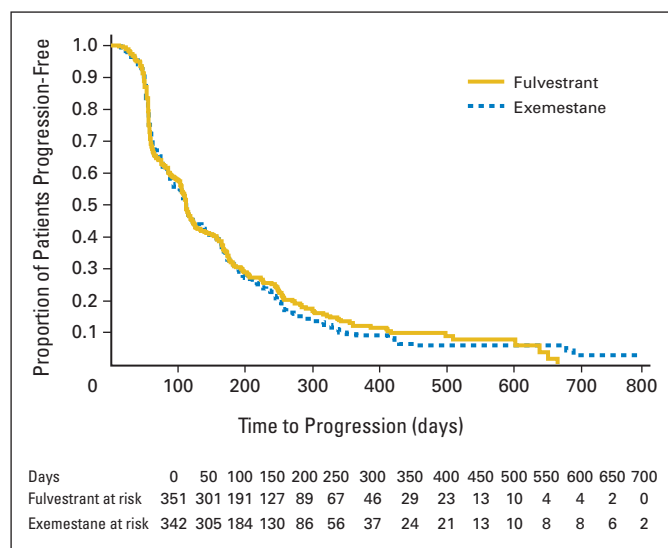


Fig 1. Kaplan-Meier estimates for time to progression (TTP). Estimated median TTP for patients receiving fulvestrant was 3.7 months, compared with 3.7 months for patients receiving exemestane (hazard ratio = 0.963; 95% CI, 0.819 to 1.133; *P* = .6531).

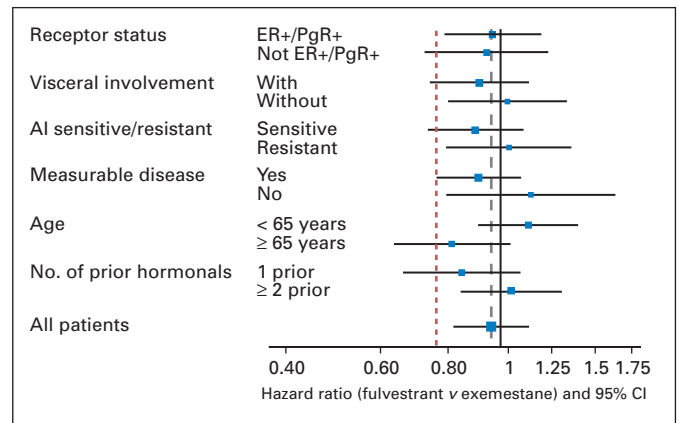


Fig 2. Forest plot of effect of predefined covariates on time to progression. ER, estrogen receptor; PgR, progesterone receptor.

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 EFACT 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 EFACT 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

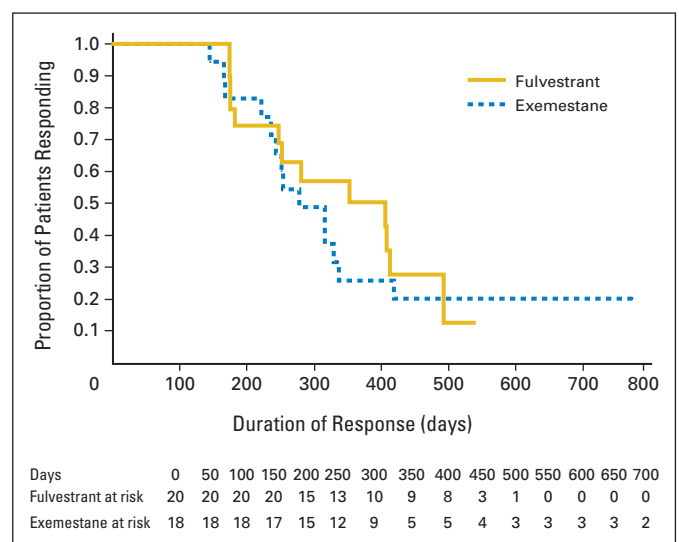


Fig 3. Kaplan-Meier estimates for duration of response (DOR; from random assignment). Estimated median DOR for patients receiving fulvestrant was 13.5 months, compared with 9.8 months for patients receiving exemestane.

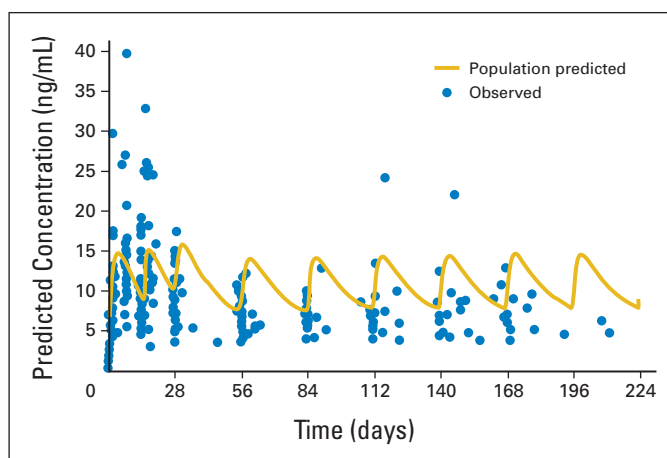


Fig 4. Observed and population-predicted pharmacokinetic profile for the fulvestrant loading-dose regimen (500 mg day 0, 250 mg day 14, 250 mg day 28, and then 250 mg/month thereafter).

of fulvestrant and an AI compared with an AI alone is another approach being studied in several clinical trials. The premise for the combination is that fulvestrant may be more effective in a low-estrogen environment, which is supported by preclinical data.³³

In conclusion, EFFECT has demonstrated clinical activity for both LD fulvestrant and exemestane in a meaningful proportion of postmenopausal HR+ ABC after progression during treatment with a nonsteroidal AI. Both agents were well tolerated, with a similar incidence of reported adverse events and quality of life. There were also no apparent preliminary differences in the proportion of women receiving chemotherapy (approximately 50%) as the first subsequent systemic therapy after trial treatment failure. The pros and cons of these two agents with their different mechanisms of action, costs, and modes of delivery should be discussed with patients because there are preferences to both intramuscular and oral agents.³⁴

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: Pamela Rennie, AstraZeneca (C); Francisco Sapunar, AstraZeneca (C); Elizabeth Lowe, AstraZeneca (C)

Consultant or Advisory Role: Stephen Chia, Advisory board for AstraZeneca (C); William Gradishar, AstraZeneca (C), Pfizer (C); Louis Mauriac, Novartis (C), AstraZeneca (C); John F.R. Robertson, AstraZeneca (C), Pfizer (C); Martine Piccart, AstraZeneca (C), Pfizer (C), Novartis (C) **Stock Ownership:** Pamela Rennie, AstraZeneca; Francisco Sapunar, AstraZeneca; Elizabeth Lowe, AstraZeneca

Honoraria: Stephen Chia, Honoraria for CME talks by AstraZeneca; Louis Mauriac, Novartis, AstraZeneca; Jose Bines, AstraZeneca; Aman Buzdar, AstraZeneca, Eli Lilly, Roche, Genetech, Pfizer, Taiho; John F.R. Robertson, AstraZeneca; Adam Brufsky, AstraZeneca; Kurt Possinger, AstraZeneca **Research Funding:** Stephen Chia, Investigator initiated funding with AstraZeneca; William Gradishar, AstraZeneca; John F.R. Robertson, AstraZeneca; Martine Piccart, Novartis, Pfizer **Expert**

Testimony: None **Other Remuneration:** John F.R. Robertson, AstraZeneca, Pfizer; Kurt Possinger, AstraZeneca

AUTHOR CONTRIBUTIONS

Conception and design: Stephen Chia, Aman Buzdar, Pamela Rennie, Francisco Sapunar

Provision of study materials or patients: Stephen Chia, William Gradishar, Louis Mauriac, Jose Bines, Frederic Amant, Miriam Federico, Luis Fein, Gilles Romieu, Aman Buzdar, John F.R. Robertson, Adam Brufsky, Kurt Possinger, Martine Piccart

Collection and assembly of data: Stephen Chia, William Gradishar, Louis Mauriac, Frederic Amant, John F.R. Robertson, Adam Brufsky, Pamela Rennie, Elizabeth Lowe

Data analysis and interpretation: Stephen Chia, William Gradishar, Aman Buzdar, John F.R. Robertson, Adam Brufsky, Pamela Rennie, Francisco Sapunar, Elizabeth Lowe, Martine Piccart

Manuscript writing: Stephen Chia, William Gradishar, Frederic Amant, Aman Buzdar, John F.R. Robertson, Adam Brufsky, Pamela Rennie, Elizabeth Lowe

Final approval of manuscript: Stephen Chia, William Gradishar, Louis Mauriac, Jose Bines, Frederic Amant, Miriam Federico, Luis Fein, Gilles Romieu, Aman Buzdar, John F.R. Robertson, Adam Brufsky, Kurt Possinger, Pamela Rennie, Francisco Sapunar, Elizabeth Lowe, Martine Piccart

REFERENCES

- Jatoi I, Chen BE, Anderson WF, et al: Breast cancer mortality trends in the United States according to estrogen receptor status and age at diagnosis. *J Clin Oncol* 25:1683-1690, 2007
- Bonneterre J, Buzdar A, Nabholz JMA, et al: Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma: Results of two randomized trials designed for combined analysis. *Cancer* 92:2247-2258, 2001
- Mouridsen H, Gershonovich M, Sun Y, et al: Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 21:2101-2109, 2003
- Paridaens R, Dirix L, Lohrisch C, et al: Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol* 14:1391-1398, 2003
- Howell A, Cuzick J, Baum M, et al: Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 365:60-62, 2005
- Thürlimann B, Keshaviah A, Coates AS: A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 353:2747-2757, 2005
- Coomes RC, Hall E, Gibson LJ, et al: A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 350:1081-1092, 2004
- Jakesz R, Jonat W, Gnani M, et al: Switching of postmenopausal women with endocrine responsive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: Combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 366:455-462, 2005
- Goss PE, Ingle JN, Martino S, et al: A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early stage breast cancer. *N Engl J Med* 349:1793-1802, 2003
- Winer EP, Hudis C, Burstein HJ, et al: American Society of Clinical Oncology technology assessment of the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor positive breast cancer: Status report 2004. *J Clin Oncol* 23:619-629, 2005
- Wakeling AE, Dukes M, and Bowler J: A potent specific pure antiestrogen with clinical potential. *Cancer Res* 51:3867-3873, 1991

12. 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
13. Robertson JFR, Nicholson RI, Bundred NJ, et al: Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)-nonyl]estra-1,3,5,(10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with primary breast cancer. *Cancer Res* 61:6739-6746, 2001
14. Osborne CK, Pippen 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
15. Howell A, Robertson JFR, Albano JQ, et al: Fulvestrant, formerly ICI 182,780, is effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol* 20:3396-3403, 2002
16. Howell A, Robertson JFR, Abram P, et al: Comparison of fulvestrant versus tamoxifen for the treatment of advanced breast cancer in postmenopausal women previously untreated with endocrine therapy: A multinational, double blind randomized trial. *J Clin Oncol* 22:1605-1613, 2004
17. Ingle JN, Suman VJ, Rowland KM, et al: Fulvestrant in women with advanced breast cancer after progression on prior aromatase inhibitor therapy: North Central Cancer Treatment Trial Group Trial N0032. *J Clin Oncol* 24:1052-1056, 2006
18. Perey L, Paridaens R, Hawle H, et al: Clinical benefit of fulvestrant in postmenopausal women with advanced breast cancer and primary or acquired resistance to aromatase inhibitors: Final results of phase II Swiss Group for Clinical Cancer Res Trial (SAKK 21/00). *Ann Oncol* 18:64-69, 2007
19. Miki Y, Suzuki T, Hatori M, et al: Effects of aromatase inhibitors on human osteoblast and osteoblast-like cells: A possible androgenic bone protective effects induced by exemestane. *Bone* 40:876-887, 2007
20. Lønning PE, Bajetta E, Murray R, et al: Activity of exemestane in metastatic breast cancer after failure of nonsteroidal aromatase inhibitors: A phase II trial. *J Clin Oncol* 18:2234-2244, 2000
21. Robertson JFR, Osborne CK, Howell A, et al: Fulvestrant versus anastrozole for the treatment of advanced breast cancer in postmenopausal women: A prospective combined analysis of two multicentre trials. *Cancer* 98:229-238, 2003
22. Robertson JF, Erikstein B, Osborne CK, et al: Pharmacokinetic profile of intramuscular fulvestrant in advanced breast cancer. *Clin Pharmacokinet* 43:529-538, 2004
23. Dauvois S, White R, Parker MG: The antiestrogen ICI 182780 disrupts estrogen receptor nucleocytoplasmic shuttling. *J Cell Sci* 106:1377-1388, 1993
24. Gibson MK, Nemmers LA, Beckman WC, et al: The mechanism of ICI 164,384 antiestrogenicity involves rapid loss of estrogen receptor in uterine tissue. *Endocrinology* 129:2000-2010, 1991
25. Osborne CK, Coronado-Heinsohn EB, Hilsenbeck SG, et al: Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer. *J Natl Cancer Inst* 87:746-750, 1995
26. Dauvois S, Danielian PS, White R, et al: Antiestrogen ICI 164,384 reduces cellular estrogen receptor content by increasing its turnover. *Proc Natl Acad Sci U S A* 89:4037-4041, 1992
27. Fawell SE, White R, Hoare S, et al: Inhibition of estrogen receptor DNA binding by the "pure" antiestrogen ICI 164,384 appears to be mediated by impaired receptor dimerization. *Proc Natl Acad Sci U S A* 87:6883-6887, 1990
28. Franco S, Perez A, Tan-Chiu E, et al: Response to fulvestrant in heavily pretreated postmenopausal women: A single-center experience. *Breast Cancer Res Treat* 88:103-108, 2004
29. Steger GG, Gips M, Simon SD, et al: Fulvestrant ('Faslodex'): Clinical experience from the compassionate use programme. *Cancer Treat Rev* 31: S10-S16, 2005 (suppl 2)
30. Mauriac L, Pippen JE, Quaresma Albano J, et al: Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of subgroups of postmenopausal women with visceral and non-visceral metastases: Combined results from two multicentre trials. *Eur J Cancer* 39:1228-1233, 2003
31. Geisler J, King N, Anker G, et al: In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. *Clin Cancer Res* 4:2089-2093, 1998
32. Geisler J, Haynes B, Anker G, et al: Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. *J Clin Oncol* 20:751-757, 2002
33. Jelovac D, Macedo L, Golubeva OG, et al: Additive antitumor effect of aromatase inhibitor letrozole and antiestrogen fulvestrant in a postmenopausal breast cancer model. *Cancer Res* 65: 5439-5444, 2005
34. Fallowfield L, Atkins L, Catt S, et al: Patients' preference for the administration of endocrine treatments by injection or tablets: Results from a study of women with breast cancer. *Ann Oncol* 17:205-210, 2006

Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).