

Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment

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Purpose: To compare the efficacy and tolerability of fulvestrant (formerly ICI 182,780) and anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment.

Patients and Methods: Patients (n = 451) with advanced breast cancer were randomized to receive fulvestrant 250 mg as a once-monthly (one × 5 mL) intramuscular injection or an oral dose of anastrozole 1 mg in this open, parallel-group, multicenter trial. The primary end point was time to progression (TTP). Secondary end points included objective response (OR) rates, defined as complete response (CR) or partial response (PR), duration of response (DOR), and tolerability.

Results: Patients were followed for a median period of 14.4 months. In terms of TTP, fulvestrant was as effective as anastrozole (hazard ratio, 0.98; confidence interval [CI], 0.80 to 1.21; P = .84). Median TTP was 5.5 months for fulvestrant and 5.1 months for anastrozole.

OR rates showed a numerical advantage for fulvestrant (20.7%) over anastrozole (15.7%) (odds ratio, 1.38; CI, 0.84 to 2.29; P = .20). Clinical benefit rates (CR + PR + stable disease ≥ 24 weeks) were 44.6% for fulvestrant and 45.0% for anastrozole. Median DOR was 15.0 months for fulvestrant and 14.5 months for anastrozole. Both treatments were well tolerated, with 3.2% and 1.3% of fulvestrant- and anastrozole-treated patients, respectively, withdrawn from treatment because of an adverse event.

Conclusion: Fulvestrant was as effective as anastrozole. These data confirm that fulvestrant is an additional, effective, and well-tolerated treatment for advanced breast cancer in postmenopausal women whose disease progressed on prior endocrine therapy.

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THE TREATMENT OF breast cancer in postmenopausal women with hormone-responsive tumors is based on two key approaches: prevention of estrogen binding to the estrogen receptor (ER) using an antiestrogen, or lowering of estrogen levels using an aromatase inhibitor. The selective estrogen receptor modulator tamoxifen (Nolvadex; AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom) is the most widely used hormonal treatment for breast cancer and has good efficacy in hormone-sensitive tumors.¹ Tamoxifen has also been shown to be highly

effective in reducing the incidence of breast cancer in patients at high risk of developing the disease.² Once breast cancer recurs or progresses after treatment with tamoxifen, standard follow-up treatments are the aromatase inhibitors, such as third-generation oral, selective aromatase inhibitors including anastrozole (Arimidex; AstraZeneca) or letrozole (Femara; Novartis Pharma AG, Basel, Switzerland).

A specific antiestrogen with high affinity for the ER and without agonist effects may have advantages over tamoxifen in the treatment of hormone-sensitive breast cancer. Fulvestrant (Faslodex, formerly known as ICI 182,780; AstraZeneca) is a novel, steroidal, ER downregulator with a mode of action distinct from that of tamoxifen.³ Fulvestrant binds to the ER and a rapid loss of ER protein in the tumor ensues.⁴ This downregulation of the ER levels in the tumor is dose dependent, as is the significant reduction in tumor progesterone receptor (PgR) levels.⁴ Tamoxifen, in contrast, is associated with a rise in PgR levels, which demonstrates the presence of a functional estradiol pathway and confirms the partial agonism of tamoxifen in contrast to the “pure” antagonist action of fulvestrant. Preclinical studies indicated that fulvestrant would be effective in tamoxifen-resistant breast cancer.⁵ A phase II trial conducted with fulvestrant in women with advanced breast cancer resistant to tamoxifen^{6,7} demonstrated that fulvestrant has good clinical activity in tamoxifen-resistant breast cancer and also sug-

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gested a prolonged duration of response (DOR) when compared indirectly with a matched group of patients who received megestrol acetate after failure of tamoxifen.⁷

This article reports the results of an open, randomized, multicenter, parallel-group, phase III clinical trial that compared the efficacy and tolerability of fulvestrant 250 mg administered as a once-monthly intramuscular (IM) injection with an oral dose of anastrozole 1 mg once daily, in postmenopausal women with advanced breast cancer whose disease had progressed after prior endocrine therapy.

PATIENTS AND METHODS

Study Design

This was an open, randomized, international, multicenter, parallel-group, phase III trial. It was originally designed to compare two doses of fulvestrant (125 mg and 250 mg per month IM) with a single dose of anastrozole (1 mg/d orally). The study (trial 0020) was carried out in Europe, Australia, and South Africa and involved 83 centers. In this open trial, fulvestrant 250 mg was given as a one \times 5-mL injection, compared with the two \times 2.5-mL injections that were administered in the North American trial 0021. Trial 0021 was a double-blind, double-dummy trial using the same drug doses and a similar protocol that ran concurrently, also appearing in the August 15, 2002, issue of the *Journal of Clinical Oncology*.⁸ These trials were designed to be evaluated individually and using combined data.

A preliminary data summary and an interim analysis were planned and conducted because the clinical activity of fulvestrant 125 mg had not been previously tested. Therefore, both trials included a preliminary data summary stage after the first 30 subjects in the fulvestrant 125-mg group (combined from both trials) had been treated and followed up for a minimum of 3 months. This interim assessment showed insufficient evidence of clinical activity for the 125-mg dose of fulvestrant, with no objective tumor responses. The independent data monitoring committee therefore recommended that recruitment to the fulvestrant 125-mg treatment arm be stopped. Patients already recruited into the 125-mg arm in this trial were permitted to remain on fulvestrant 125 mg or be withdrawn from the trial and returned to other treatments at the discretion of their clinician. These patients were not monitored further for efficacy. As a consequence of dropping this treatment arm, the protocol for the study was amended to be a comparison between fulvestrant 250 mg (IM) and anastrozole 1 mg/d orally.

An interim analysis was conducted when 170 disease progressions or deaths had occurred across the remaining arms and time to progression (TTP) was formally analyzed. Objective response (OR) rate (defined as complete response [CR] + partial response [PR], using Union Internationale Contre le Cancer criteria) and adverse event (AE) data were summarized. As a result of the interim analysis, the independent data monitoring committee recommended that both trials should continue.

Fulvestrant 250 mg (IM) was compared with anastrozole (1 mg/d given orally) in terms of the primary end point of TTP. Secondary end points included OR, DOR, time to treatment failure (TTF), time to death (TTD), and tolerability. Other secondary end points were quality of life, symptomatic response, and pharmacokinetics. Other efficacy datapoints reported included clinical benefit (CR + PR + stable disease [SD] \geq 24 weeks), and duration of clinical benefit. All data are reported here except for pharmacokinetics, which will be reported elsewhere.

Patient Population

All patients were postmenopausal women with locally advanced or metastatic breast cancer whose disease had progressed during adjuvant endocrine therapy or first-line endocrine therapy for advanced disease. All women had tumors with evidence of hormone sensitivity (ie, prior sensitivity to hormonal therapy or known ER or PgR positivity) and life expectancy of greater than 3 months, and in the opinion of the investigator, all were deemed appropriate candidates for subsequent hormonal therapy.

For inclusion in the trial, patients had to have a World Health Organization performance status of \leq 2, histologic or cytologic confirmation of breast cancer, and objective evidence of recurrence or progression of disease that was not amenable to curative treatment, with the presence of at least one measurable or assessable (nonmeasurable) lesion. All patients had to be postmenopausal (ie, \geq 60 years old or aged \geq 45 years with amenorrhea for $>$ 12 months or follicle-stimulating hormone levels within postmenopausal range, or having undergone bilateral oophorectomy).

Exclusion criteria included the following: presence of life-threatening metastatic visceral disease (defined as extensive hepatic involvement) or any degree of brain or leptomeningeal involvement or symptomatic pulmonary lymphangitic spread; prior treatment for breast cancer with fulvestrant or any aromatase inhibitor; more than one prior endocrine treatment for advanced breast cancer; extensive radiation therapy or cytotoxic treatment within the past 4 weeks; estrogen replacement therapy within 4 weeks of randomization; treatment with luteinizing hormone-releasing hormone analogs within 3 months of randomization; and any concurrent medical illness or laboratory abnormalities that would compromise safety or prevent interpretation of results.

Subjects taking bisphosphonates were permitted to enter the trial but their bone lesions were not considered to be assessable for response, although they were assessable for progression. Initiation of bisphosphonate treatment during the trial was discouraged. If bisphosphonates were commenced in the absence of objective evidence of progression, bone lesions were assessed only for progression.

All patients gave written informed consent, and approval was obtained from the relevant ethical committees.

Trial Treatments

Fulvestrant was supplied in vials as a single-dose, castor oil-based, 5% solution. Each vial contained 250 mg of fulvestrant at a concentration of 50 mg/mL in a volume of 5 mL. Fulvestrant 250 mg was administered slowly by a single one \times 5-mL injection into the buttock. Injections were given once a month, which was defined as every 28 days (\pm 3 days). Anastrozole 1 mg was supplied as round, white, film-coated tablets and administered orally once daily.

Patients continued treatment until objective disease progression or other events required withdrawal. At such time, trial treatment was stopped and standard therapy was initiated. Thereafter, patients were followed up until death. Patients who withdrew from trial treatment before disease progression were followed up until objective disease progression and death.

For all patients, objective tumor assessments were undertaken every 3 months until evidence of either objective disease progression or death. Patients with skin or soft tissue lesions were also assessed every month during the first 3 months of treatment.

Statistical Methodology

The trial was designed to detect the superiority of fulvestrant 250 mg in terms of efficacy compared with anastrozole 1 mg. The final analysis was scheduled to occur when 340 events (ie, objective disease progression or death) had occurred across the two groups. This provided 90% power to detect a hazard ratio (HR) ≥ 1.43 or ≤ 0.70 for fulvestrant treatment compared with anastrozole treatment, at a significance level of 5%. To achieve the required number of events, it was calculated that 392 patients (196 in each treatment group) would be required.

The efficacy analyses were performed according to randomized treatment (ie, "intention to treat") using a nominal significance level of 5%. However, for the TTP and OR analyses, the significance level was adjusted to 4.86% because of the preliminary data summary of OR and the interim analysis of TTP. As a result, the 95% confidence intervals (CIs) were adjusted accordingly to 95.14%. All significance levels were two-sided.

Although not described in the protocol, fulvestrant was retrospectively compared with anastrozole for noninferiority for OR, TTP and TTF. Because of the interim analysis, a one-sided CI of 97.57% was used for the analyses of TTP and OR. For TTF, a one-sided CI of 97.5% was used. These limits are identical to using the upper limit of the 95.14% two-sided CI from the analysis of TTP, the lower limit of the 95.14% two-sided CI for the difference in response rates for OR, and the upper limit of the 95% two-sided CI for TTF.

For previous United States regulatory submissions of hormonal treatments for advanced breast cancer, the requirements for showing noninferiority for TTP were based on the upper one-sided confidence limit for the TTP HR not being greater than 1.25 (ie, a potential deficiency of $> 25\%$ for the experimental treatment had to be ruled out). In the same submissions, the requirement for demonstrating noninferiority in terms of response rate was based on ruling out a deficiency in the difference in response rates of greater than 10%. Consequently, these criteria have been used to assess noninferiority of fulvestrant relative to anastrozole in this trial.

TTP. TTP was defined as the time from randomization until objective disease progression. Death was regarded as a progression event in those who died before disease progression. Subjects whose disease had not progressed at the time of analysis were right-censored using the last assessment date. Treatments were compared using the Cox proportional hazards regression model (including the covariates age, performance status, measurable compared with nonmeasurable disease, receptor status, previous response to hormone therapy, previous use of cytotoxic chemotherapy, and use of bisphosphonate therapy for bone disease). A global test was performed to determine whether there were significant treatment-by-baseline covariate interactions. The estimate of the treatment effect is expressed as an HR (fulvestrant/anastrozole), together with the corresponding CI and P value. TTP was also summarized using Kaplan-Meier curves for each treatment group, and the median TTP was calculated.

TTF. TTF was defined as the number of days from randomization until the earliest occurrence of disease progression, death from any cause, or withdrawal from trial treatment for any reason. Patients who had not experienced treatment failure at the time of analysis were right-censored in the analysis at the time of their last assessment. Any patient who did not receive any trial therapy was assigned an uncensored TTF of zero days. Statistically, TTF was analyzed in the same way as TTP.

OR rate. Responders were defined as those patients with CR or PR. To qualify as a responder, the patient had to satisfy the criteria for CR

or PR on one visit with no evidence of disease recurrence or death within 4 weeks of the response assessment. Treatment differences in OR were assessed by comparing the proportion of responders (CR and PR) using a logistic regression model (with the same covariates as for TTP). The estimate of the treatment effect is expressed as an odds ratio (fulvestrant/anastrozole), together with the corresponding CI and P value. In addition, an estimate of the difference in response rates (fulvestrant/anastrozole) and corresponding CI was also produced.⁹

DOR. The DOR was defined, for responding patients only, as the period of time from randomization to the first observation of disease progression. Patients who died before reaching progression were classed as completing their response at time of death. The DOR was summarized using Kaplan-Meier curves for each treatment group, and the median DOR was also calculated for each group.

No statistical comparison was performed for DOR in only those patients responding to treatment, since this is not a randomized comparison. Rather, all patients were included in a statistical analysis of DOR, defined for responders as the time from the onset of response to disease progression and for nonresponders as zero. These data were also summarized using Kaplan-Meier curves.

Clinical benefit. Clinical benefit was defined by the sum of CR + PR + SD ≥ 24 weeks. Although a formal analysis of clinical benefit was not protocolled, treatment differences in the rate of clinical benefit were retrospectively assessed in the same way as that of OR rate. The duration of clinical benefit was presented as for DOR.

TTD. TTD was protocolled to be analyzed when at least 50% of the patients had died. At the time of data analysis, only 36.7% of patients had died and therefore no formal statistical analyses were made at this time.

Tolerability

Any detrimental change in a patient's condition subsequent to them entering onto the trial and during the follow-up period after the final treatment (8 weeks after last injection of fulvestrant and 30 days after the last day of treatment with anastrozole), which was not unequivocally due to progression of disease, was considered to be an AE. All safety data were listed and summarized according to the treatment received. No formal statistical analyses were performed on the safety data from this individual trial. However, a planned statistical analysis of predefined AEs was performed on the combined data from this trial and the North American trial; this will be reported elsewhere. The most common AEs (occurring at incidence of $\geq 10\%$) and most common drug-related AEs are reported here by treatment received.

Quality of Life

Quality of life (QOL) was assessed using the Functional Assessment of Cancer Therapy (FACT)-Breast questionnaire, which comprises the FACT-General QOL tool for cancer patients plus the breast cancer subscale. This questionnaire has been extensively validated in respect to its psychometric properties and sensitivity to clinical changes^{10,11} and is in use in a number of large breast cancer treatment trials in the United States and Europe.

The analysis was undertaken on data collected up to the date of progression, using the trial outcome index (TOI) within the FACT-Breast. This measure is the sum of the functional well-being, physical well-being and breast cancer subscale dimensions of the questionnaire. Patients without baseline TOI data or with data collected more than 7 days after the start of treatment were excluded from this analysis.

The difference in TOI over time between the fulvestrant 250-mg group and the anastrozole 1-mg group was compared using a general-

Table 1. Demographic and Pretreatment Characteristics

Characteristic	Fulvestrant 250 mg (n = 222)		Anastrozole 1 mg/d (n = 229)	
	No.	%	No.	%
Age, years				
Mean	63		64	
Range	35-86		33-89	
Weight, kg				
Mean	69		68	
Range	41-124		40-110	
Prior treatment				
Cytotoxic chemotherapy	94	42.3	98	42.8
Endocrine therapy for advanced disease	126	56.8	129	56.3
Adjuvant endocrine therapy	121	54.5	119	52.0
Hormone receptor status				
ER and/or PgR+ve	163	73.4	183	79.9
ER/PgR unknown	51	23.0	37	16.2
ER/PgR-ve	8	3.6	9	3.9
Metastatic or recurrent disease at baseline				
Breast	21	9.5	30	13.1
Skin	40	18.0	35	15.3
Bone	115	51.8	117	51.1
Liver	48	21.6	56	24.5
Lung	56	25.2	60	26.2
Lymph nodes	78	35.1	83	36.2
Other	27	12.2	18	7.9
Extent of metastatic or recurrent disease at baseline				
Soft tissue only	11	5.0	8	3.5
Bone only	38	17.1	40	17.5
Visceral only	30	13.5	41	17.9
Lymph node only	22	9.9	21	9.2
Not recorded	0	0	1	0.4
Mixed*	121	54.5	118	51.5
Measurable lesions†	131	59.0	142	62.0
Nonmeasurable lesions	91	41.0	87	38.0

NOTE. Patients may be in more than one category.

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

*Mixed is defined as breast and/or a combination of skin, bone, liver, lung, or lymph nodes.

†Measurable lesions were lesions that were clinically measurable in two perpendicular axes with at least one dimension being ≥ 2.5 cm or measurable using imaging in two perpendicular axes with at least one dimension being ≥ 1.0 cm.

ized linear mixed model (ie, a random coefficients model) with the same covariates as for TTP. A graph of the mean TOI (\pm standard deviation) over time was also produced.

RESULTS

Patients

A total of 451 patients were randomized to fulvestrant 250 mg (n = 222) or to anastrozole 1 mg once daily (n = 229) and were followed for a median period of 14.4 months. The majority of patients (97% in the fulvestrant group and 98% in the anastrozole group) had previously been treated with tamoxifen as either adjuvant therapy or for advanced disease. The other patients were previously treated with droloxifene, goserelin, idoxifene, megestrol acetate, or toremifene. A total of

95 patients in the fulvestrant group and 100 patients in the anastrozole group had only received endocrine therapy as adjuvant treatment. Of these, the majority (80.0%) stopped treatment less than 365 days before randomization.

The characteristics of the patients in the two treatment groups are given in Table 1. Patients in the fulvestrant and the anastrozole groups were well matched in terms of age, weight, breast cancer history, and ER/PgR status. Only 11.8% of patients in the fulvestrant group and 7.5% of patients in the anastrozole group had bisphosphonate therapy.

Efficacy

TTP. At the time of analysis, 183 (82.4%) of 222 of those patients randomized to fulvestrant had progressed, as

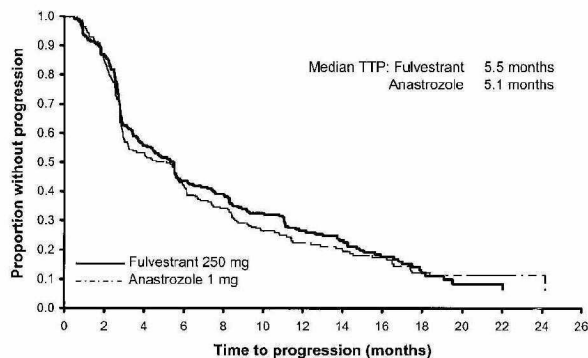


Fig 1. Kaplan-Meier estimates for time to progression.

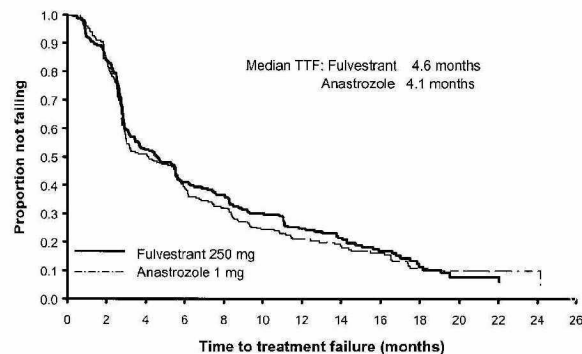


Fig 2. Kaplan-Meier estimates for time to treatment failure.

had 191 (83.4%) of 229 of those randomized to anastrozole. The statistical analysis showed that there was no evidence of a statistically significant difference in TTP between fulvestrant and anastrozole (HR, 0.98; 95.14% CI, 0.80 to 1.21; $P = .84$). The 95.14% CI indicates that the risk of progression for patients randomized to fulvestrant 250 mg could be between 20% lower and 21% higher than it is for patients randomized to anastrozole. These data fulfill the criteria for noninferiority of fulvestrant relative to anastrozole. The Kaplan-Meier curves for TTP with fulvestrant and anastrozole are shown in Fig 1. The median TTP was 5.5 months for fulvestrant and 5.1 months for anastrozole.

TTF. At the trial cutoff date, 188 patients (84.7%) in the fulvestrant group and 196 patients (85.6%) in the anastrozole group had experienced treatment failure. The statistical analysis showed that fulvestrant was not significantly different from anastrozole in terms of TTF (HR, 0.97; 95% CI, 0.80 to 1.19; $P = .81$) (Fig 2), and the criteria for noninferiority of fulvestrant were fulfilled. The median TTF was 4.6 months for fulvestrant and 4.1 months for anastrozole. Of those patients whose treatment failed, 94.7% of the fulvestrant group and 95.4% of the anastrozole group experienced treatment failure because of disease progression. Other reasons for treatment failure included AEs (fulvestrant v anastrozole, 1.6% v 1.5%), protocol noncompliance (1.1% v 2.0%), and withdrawal of informed consent (1.1% v 0.5%).

OR rate. At the time of data cutoff, 20.7% of patients in the fulvestrant group and 15.7% of those in the anastrozole group had evidence of OR (ie, had a best OR of CR or PR) (Table 2). The statistical analysis for OR showed no statistically significant difference between fulvestrant and anastrozole (difference in response rates, 4.8%; 95.14% CI, -2.19% to 14.23%), and the criteria for noninferiority of fulvestrant were fulfilled. There was a nonsignificant numerical advantage for fulvestrant over anastrozole, with the

odds of attaining OR being 38% higher in the fulvestrant group (odds ratio, 1.38; 95.14% CI, 0.84 to 2.29; $P = .20$).

Clinical benefit rates (CR + PR + SD \geq 24 weeks) of 44.6% and 45.0% were observed for fulvestrant and anastrozole, respectively (Table 2), with the analysis showing no statistically significant difference (difference in clinical benefit rates, -0.95% ; 95% CI, -10.12% to 8.64% ; $P = .85$).

Further follow-up was performed to obtain more complete information for DOR (median follow-up, 22.6 months). The median DOR, as measured from randomization to progression, in those patients who responded to treatment was 15.0 months for fulvestrant ($n = 48$) and 14.5 months for anastrozole ($n = 39$). Kaplan-Meier curves for

Table 2. Best Objective Responses for Fulvestrant, 250 mg IM or Anastrozole 1 mg Orally od

	Fulvestrant (n = 222)		Anastrozole (n = 229)	
	No.	%	No.	%
CR	10	4.5	4	1.7
PR	36	16.2	32	14.0
Total (OR)	46	20.7*	36	15.7
SD \geq 24 weeks	53	23.9	67	29.3
SD < 24 weeks	3	1.4	3	1.3
Not progressed†	10	4.5	6	2.6
Progressed	110	49.5	117	51.1
Total	176	79.3	193	84.3
Clinical benefit (CR + PR + SD \geq 24 weeks)	99	44.6‡	103	45.0

Abbreviations: CR, complete response; PR, partial response; SD, stable disease.

*Difference in response rates, 4.8%; 95.14% CI, -2.19% to 14.23% .

†Patients with a best response of "not progressed" were not assessable for response except for progression (eg, patients with bone-only disease taking bisphosphonates).

‡Difference in clinical benefit rates, -0.95% ; 95% CI, -10.12% to 8.64% ; $P = .85$.

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