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

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<u>Purpose</u>: To compare the efficacy and tolerability of fulvestrant (formerly ICI 182,780) with anastrozole in the treatment of advanced breast cancer in patients whose disease progresses on prior endocrine treatment.

Patients and Methods: In this double-blind, double-dummy, parallel-group study, postmenopausal patients were randomized to receive either an intramuscular injection of fulvestrant 250 mg once monthly or a daily oral dose of anastrozole 1 mg. The primary end point was time to progression (TTP). Secondary end points included objective response (OR) rate, duration of response (DOR), and tolerability.

<u>Results:</u> Patients (n = 400) were followed for a median period of 16.8 months. Fulvestrant was as effective as anastrozole in terms of TTP (hazard ratio, 0.92; 95.14% confidence interval [CI], 0.74 to 1.14; P = .43); median TTP was 5.4 months with fulvestrant and 3.4 months with anastrozole. OR rates were 17.5% with both treatments. Clinical benefit rates (complete re-

sponse + partial response + stable disease \geq 24 weeks) were 42.2% for fulvestrant and 36.1% for anastrozole (95% CI, -4.00% to 16.41%; P=.26). In responding patients, median DOR (from randomization to progression) was 19.0 months for fulvestrant and 10.8 months for anastrozole. Using all patients, DOR was significantly greater for fulvestrant compared with anastrozole; the ratio of average response durations was 1.35 (95% CI, 1.10 to 1.67; P<0.01). Both treatments were well tolerated.

<u>Conclusion</u>: Fulvestrant was at least as effective as anastrozole, with efficacy end points slightly favoring fulvestrant. Fulvestrant represents an additional treatment option for postmenopausal women with advanced breast cancer whose disease progresses on tamoxifen therapy.

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THE SELECTIVE estrogen receptor modulator (SERM) tamoxifen (Nolvadex; AstraZeneca, Wilmington, DE) is well established as a highly effective treatment for preand postmenopausal patients with either advanced or early breast cancer. Tamoxifen has also been shown to be effective in reducing the incidence of breast cancer in patients at risk of developing the disease² and in women

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with ductal carcinoma-in-situ.3 Patients who have tumor progression or develop resistance to tamoxifen are often treated with second-line hormonal therapy. The treatment options currently available comprise the third generation of oral, selective nonsteroidal aromatase inhibitors including anastrozole, letrozole, and the steroidal agent exemestane. Fulvestrant (Faslodex; AstraZeneca, Macclesfield, United Kingdom) is a "pure" estrogen antagonist with a novel mode of action, distinct from that of tamoxifen or any other antiestrogen currently available. Fulvestrant, like tamoxifen, binds to estrogen receptors (ERs) competitively. However, in contrast to tamoxifen, fulvestrant's binding leads to rapid degradation and loss of ER protein.4 Furthermore, fulvestrant antagonizes all of the transactivating functions of the receptor, whereas tamoxifen blocks only one, a feature that contributes to its estrogen agonist activity in some tissues.⁴ Accordingly, fulvestrant is the first in a new class of antiestrogens-an ER downregulator-and is devoid of agonist activity.5 Fulvestrant has greater potency than tamoxifen at inhibiting the growth of breast tumors and doubles the time to the development of resistance in a xenograft murine model of human breast cancer.⁶ It also inhibits growth of tamoxifen-resistant tumors in this mod-

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el.⁶ In primary breast cancer patients who received a single injection of fulvestrant (at doses of 50, 125, or 250 mg) 14 to 21 days before the initial tumor resection, fulvestrant produced a dose-dependent reduction in both ER and progesterone receptor (PgR) expression. In contrast, a separate group of patients in the same study who received tamoxifen 20 mg orally before tumor resection showed an increase in PgR expression, thereby confirming the partial estrogen agonist activity of tamoxifen. A phase II study in postmenopausal women with advanced breast cancer whose disease progresses after tamoxifen therapy given as adjuvant or for advance disease showed that subsequent treatment with fulvestrant was associated with durable responses. ⁸⁻¹⁰

This study provides the first opportunity to compare the relative efficacy of ER suppression with the ER downregulator fulvestrant with that of anastrozole, as second-line therapy in patients with potentially hormone-dependent advanced breast cancer.

PATIENTS AND METHODS

Study Design

The study (trial 0021) was a randomized, double-blind, double-dummy, phase III trial conducted in North America. The trial was originally designed to compare two doses of fulvestrant (125 mg and 250 mg per month) as an intramuscular injection with anastrozole as a 1 mg/d oral dose. A nonblinded, open-label trial using the same drug doses and a similar protocol (trial 0020) was conducted concurrently in Europe, South Africa, and Australia (see accompanying article in this issue of the Journal of Clinical Oncology). 11

A preliminary data summary and an interim analysis were planned and conducted to determine the clinical activity of fulvestrant 125 mg, which 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 3 months. This interim assessment showed insufficient evidence of clinical activity for fulvestrant 125 mg with no objective tumor responses at 3 months. 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 trial 0021 were permitted to remain on fulvestrant 125 mg or withdraw from the trial and be placed on other treatments at the discretion of their clinician. These patients were not monitored further for efficacy. The lack of an objective response in the low-dose fulvestrant arm also suggests that response due to tamoxifen withdrawal in this study must be uncommon. As a consequence of dropping this treatment arm, the protocol for the study was amended to compare fulvestrant 250 mg with anastrozole 1 mg.

An interim analysis was conducted when 170 progressions or deaths had occurred across the remaining arms and time to progression (TTP) was formally analyzed. The rate of objective response (OR; 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 the trial should continue.

The primary end point of the comparison between the two drugs was TTP. Secondary end points included OR, duration of response (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 end points included clinical benefit (CR + PR + stable disease [SD] \geq 24 weeks) and duration of clinical benefit. All data are reported here except pharmacokinetics, which will be reported elsewhere.

Patient Population

All patients were postmenopausal women with locally advanced or metastatic breast cancer whose disease had progressed on adjuvant endocrine therapy with an antiestrogen or whose disease had progressed after first-line endocrine therapy for advanced disease. All women had a life expectancy of longer than 3 months and tumors with evidence of hormone sensitivity (ie, prior sensitivity to hormonal therapy or known ER or PgR positivity).

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

Exclusion criteria included the following: the presence of life-threatening metastatic visceral disease (defined as extensive hepatic involvement) or any degree of brain or leptomeningeal involvement; symptomatic pulmonary lymphangitic spread; prior treatment for breast cancer with fulvestrant or any aromatase inhibitor; more than one prior endocrine medical 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 before randomization; and any concurrent medical illness or laboratory abnormalities that would compromise safety or prevent interpretation of results.

Subjects taking bisphosphonates for bone disease 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 but allowed in the absence of objective evidence of progression. If bisphosphonates were commenced, bone lesions were assessed only for progression.

All patients provided written informed consent, and the relevant ethical committees approved the studies.

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. The matched placebo was 5 mL of the oily excipient. Fulvestrant 250 mg or matching placebo was administered slowly as a 2.5-mL injection into each buttock. Injections were given once a month, which was defined as every 28 days (± 3 days).

Anastrozole (Arimidex) 1 mg and matching placebo were supplied as round, white, film-coated tablets and administered orally once daily. Medical personnel saw all patients on a monthly basis because all patients required fulvestrant or placebo injections.



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

All patients were seen by a physician to make objective tumor assessments every 3 months until evidence of either objective disease progression or death. Patients with skin and 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 and tolerability compared with anastrozole 1 mg in postmenopausal women with advanced breast cancer.

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%. It was therefore planned to recruit 392 patients (196 in each treatment group) to achieve the required number of events.

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 are 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 evaluation of TTP and OR. For the analysis of 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 more 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 or death from any cause before progression. Subjects who had not progressed at the time of analysis were right-censored using the last assessment date. Treatments were compared using Cox's proportional hazards regression model (including the covariates age, performance status, measurable compared with non-measurable 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 was 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 whose treatment had not failed 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 a 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 after assessment. Treatment differences in OR were assessed by comparing the proportion of responders 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.

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 classified 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, because this is not a randomized comparison. Rather, all patients were included in a statistical analysis of DOR, defined for responders as the time from 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 as the sum of $CR + PR + SD \ge 24$ weeks. Although a formal analysis of clinical benefit was not protocoled, 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. As specified in the protocol, TTD (overall survival) will be analyzed when more than 50% of the patients have died. At the time of this data analysis, only 34.5% of patients had died; therefore, no formal statistical analyses were conducted.

Tolerability

Any detrimental change in a patient's condition subsequent to them entering the trial and during the follow-up period after the final treatment (8 weeks after last injection or 30 days after the last tablet, whichever was the greater), which was not unequivocally due to progression of disease, was considered to be an AE. 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 multinational trial; this will be reported elsewhere. The most common AEs (occurring at an incidence of ≥ 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 is composed of the FACT-General QOL tool for cancer patients plus the breast cancer subscale. This questionnaire has been extensively validated in respect to psychometric properties and sensitivity to clinical changes^{12,13} 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.

The difference in TOI over time between the fulvestrant 250-mg group and the anastrozole 1-mg group was compared using a generalized linear mixed model (ie, a random coefficients model) with the same covariates as for TTP. A graph of the mean TOI (± standard deviation) over time was also produced.

RESULTS

Patients

A total of 400 patients randomized to either fulvestrant 250 mg (n = 206) or to anastrozole (n = 194) were followed for a median period of 16.8 months. The majority (95% of the fulvestrant group and 96% of the anastrozole group) had been treated previously with tamoxifen either as adjuvant therapy or as initial therapy for advanced disease. Ninety-four patients in each group had received endocrine therapy as adjuvant treatment. Of these, 67 patients in the fulvestrant group and 75 patients in the anastrozole group stopped treatment less than 365 days before randomization.

The characteristics of the patients are presented in Table 1. Patients in the fulvestrant and the anastrozole groups were similar for age, weight, breast cancer history, and ER and PgR status (Table 1).

Efficacy

TTP. At the time of analysis, 83.5% of the fulvestrant group and 86.1% of the anastrozole group had experienced disease progression. There was no significant difference for TTP between the two treatment groups (HR, 0.92; 95.14% CI, 0.74 to 1.14; P = .43). The HR (0.92) indicates that the risk of progression (over a given period of time) for patients randomized to fulvestrant was 8% lower than it was for patients randomized to anastrozole. The 95.14% CI indicates that the risk of progression for patients randomized to fulvestrant 250 mg could be between 26% lower and 14% higher than it is for patients randomized to anastrozole. These data demonstrate noninferiority of fulvestrant relative to anastrozole. Median TTP was 5.4 months for fulvestrant and 3.4 months for anastrozole (Fig 1).

TTF. The majority of treatment failures were due to objective disease progression (94%), and accordingly, the Kaplan-Meier curves for TTP and TTF are very similar. For fulvestrant, there were 164 treatment failures (79.6%) because of disease progression; for anastrozole, there were 163 (84.0%). Other reasons for treatment failures included AEs, protocol noncompliance, and withdrawal of informed consent. TTF was similar for the two groups, with there being no significant difference between them

Table 1. Demographic and Pretreatment Characteristics

| | Fulvestrant 250 mg (n = 206) | | Anastrozole 1 mg/d (n = 194) | |
|--|------------------------------------|------|------------------------------------|------|
| Characteristic | No. | % | No. | % |
| Age, years | | | | |
| Mean | 63 | | 62 | |
| Range | 33-89 | | 36-94 | |
| Weight, kg | | | | |
| Mean | 72 | | 73 | |
| Range | 37-127 | | 43-134 | |
| Prior treatment | | | | |
| Cytotoxic chemotherapy | 129 | 62.6 | 122 | 62.9 |
| Endocrine therapy for advanced | 110 | 53.4 | 97 | 50.0 |
| disease | | | | |
| Adjuvant endocrine therapy | 122 | 59.2 | 116 | 59.8 |
| Hormone receptor status | | | | |
| ER and/or PgR+ve | 179 | 86.9 | 169 | 87.1 |
| ER/PgR unknown | 13 | 6.3 | 15 | 7.7 |
| ER/PgR-ve | 14 | 6.8 | 10 | 5.2 |
| Metastatic or recurrent disease at baseline | | | | |
| Breast | 8 | 3.9 | 8 | 4.1 |
| Skin | 43 | 20.9 | 41 | 21.1 |
| Bone | 90 | 43.7 | 85 | 43.8 |
| Liver | 47 | 22.8 | 45 | 23.2 |
| Lung | 63 | 30.6 | 60 | 30.9 |
| Lymph nodes | 58 | 28.2 | 56 | 28.9 |
| Other | 22 | 10.7 | 8 | 4.1 |
| Extent of metastatic or recurrent disease at | | | | |
| baseline | | | | |
| Soft tissue only | 12 | 5.8 | 13 | 6.7 |
| Bone only | 47 | 22.8 | 43 | 22.2 |
| Visceral only | 39 | 18.9 | 45 | 23.2 |
| Lymph node only | 15 | 7.3 | 17 | 8.8 |
| Not recorded | 1 | 0.5 | 2 | 1.0 |
| Mixed* | 92 | 44.7 | 74 | 38.1 |
| Measurable diseaset | 114 | 55.3 | 107 | 55.2 |
| No measurable disease | 92 | 44.7 | 87 | 44.8 |

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.

(HR, 0.96; 95% CI, 0.77 to 1.19; P = .69) (Fig 2). The data also satisfy the criteria for noninferiority. Median TTF was 4.6 months for fulvestrant (n = 206) and 3.3 months for anastrozole (n = 194).

OR rate and clinical benefit. Fulvestrant resulted in an OR in 36 patients (17.5%), while anastrozole produced an OR in 34 patients (17.5%) (Table 2). There was no statistically significant difference in OR between fulvestrant and anastrozole (difference in response rates, 0.17%; 95.14% CI, -6.31% to 9.30%). The lower CI shows



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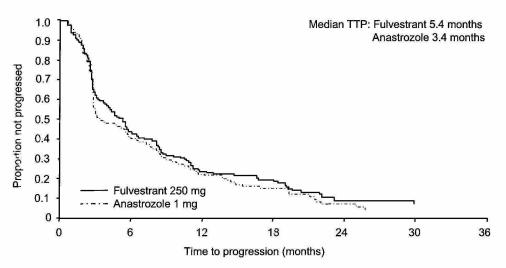


Fig 1. Kaplan-Meier estimates for time to progression.

noninferiority of fulvestrant relative to anastrozole. The odds ratio for achieving an OR in the fulvestrant group versus the anastrozole group was 1.01 (95.14% CI, 0.59 to 1.73; P = .96).

Clinical benefit rates of 42.2% and 36.1% were observed for fulvestrant and anastrozole, respectively (Table 2), with the analysis showing no statistically significant difference (difference in clinical benefit rates, 5.83%; 95% CI, -4.42% to 9.36%; P = .26).

Extended follow-up was performed in order to obtain more complete information for DOR (median follow-up, 21.3 months). The median DOR, as measured from randomization to progression, in those patients who responded to treatment was 19.0 months for fulvestrant (n=36) and 10.8 months for anastrozole (n=34). The Kaplan-Meier curves for the DOR are shown in Fig 3. In addition, DOR using all

patients—where DOR was defined as from the onset of response to disease progression for responders and zero for nonresponders—was significantly greater for fulvestrant compared with anastrozole (ratio of average response durations, 1.35; 95% CI, 1.10 to 1.67; P < .01). The Kaplan-Meier curves for DOR in all patients are shown in Fig 4. The median duration of clinical benefit was 12.9 months for fulvestrant (n = 87) and 10.9 months for anastrozole (n = 70) (Fig 5).

TTD. At the time of this data analysis, a similar number of deaths had occurred in each treatment group (fulvestrant, n = 73 [35.4%]; anastrozole, n = 65 [33.5%]). However, as specified in the protocol, TTD (overall survival) will be analyzed when more than 50% of the patients have died. Consequently, no formal statistical analyses have been conducted on these data. In

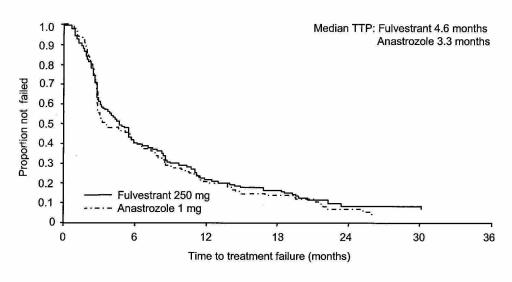


Fig 2. Kaplan-Meier estimates for time to treatment failure.



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