Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma in Postmenopausal Women

A Prospective Combined Analysis of Two Multicenter Trials

John F. R. Robertson, M.D.[1]
C. Kent Osborne, M.D.[2]
Anthony Howell, M.D.[3]
Stephen E. Jones, M.D.[4,5]
Louis Mauriac, M.D.[6]
Matthew Ellis, M.D., Ph.D.[7]
Ulrich R. Kleeberg, M.D., Ph.D.[8]
Steven E. Come, M.D.[9]
Ignace Vergote, M.D., Ph.D.[10]
Stan Gertler, M.D.[11]
Aman Buzdar, M.D.[12]
Alan Webster, M.Sc.[13]
Charles Morris, M.B., Ch.B.[13]

[1] Department of Surgery, Nottingham City Hospital, Nottingham, United Kingdom.

[2] Breast Center at Baylor College of Medicine and The Methodist Hospital, Houston, Texas.

[3] Cancer Research UK (CRUK) Department of Medical Oncology, Christie Hospital, Manchester, United Kingdom.

[4] Baylor-Sammons Cancer Center, Dallas, Texas.

[5] US Oncology Research, Houston, Texas.

[6] Bergonie Institute, Bordeaux, France.

[7] Lombardi Cancer Center, Washington, DC.

[8] Haematologische/Oncologische Praxis, Hamburg, Germany.

[9] Beth Israel Deaconess Medical Center, Boston, Massachusetts.

[10] Department of Gynaecology and Gynaecological Oncology, University Hospital of Leuven, Leuven, Belgium.

[11] Ottawa Regional Cancer Center, Ottawa, Ontario, Canada.

[12] Breast Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[13] AstraZeneca Pharmaceuticals, Macclesfield, United Kingdom.

BACKGROUND. Fulvestrant (ICI 182,780) is a new type of estrogen receptor (ER) antagonist that down-regulates the ER and has no known agonist effects. The authors report the prospectively planned combined analysis of data from 2 Phase III trials comparing fulvestrant 250 mg monthly (n = 428) and anastrozole 1 mg daily (n = 423) in postmenopausal women with advanced breast carcinoma (ABC) who previously had progressed after receiving endocrine treatment.

METHODS. The primary endpoint was time to progression (TTP). Secondary endpoints included objective response (OR), duration of response (DOR), and tolerability. The trials were designed to demonstrate superiority of fulvestrant over anastrozole. Noninferiority of fulvestrant versus anastrozole was determined using a retrospectively applied statistical test.

RESULTS. At a median follow-up of 15.1 months, ≈ 83% of patients in each treatment arm had progressed. The median TTP was 5.5 months in the fulvestrant group and 4.1 months in the anastrozole group, and the OR rates were 19.2% and 16.5% for fulvestrant and anastrozole, respectively (although the difference between treatments was not statistically significant). In patients who responded, further follow-up (median, 22.1 months) was performed to obtain more complete information on DOR; the median DOR (from randomization to disease progression) in patients who responded to treatment was 16.7 months in the fulvestrant group and 13.7 months in the anastrozole group. In a statistical analysis of DOR (using all randomized patients; from the start of response to disease progression), DOR was significantly longer for patients in the fulvestrant group compared with patients in the anastrozole group. Both drugs were tolerated well; withdrawals due to drug-related adverse events were 0.9% and 1.2% in the fulvestrant group and the

Supported by a grant from AstraZeneca Pharmaceuticals.

Dr. Robertson has received research grants and speaker's honoraria from AstraZeneca and Novartis, and he has served on the advisory board of AstraZeneca. Dr. Howell has received speaker's honoraria from and served on the advisory board of AstraZeneca. Dr. Ellis has received research grants from Genentech and Novartis and speaker's honoraria from AstraZeneca, Genentech, and Novartis; and he has performed consulting work for Johnson & Johnson and Novartis. Dr. Come has performed consulting work for and received speaker's honoraria from AstraZeneca and Novartis. Dr. Buzdar has received research grants from AstraZeneca, Bristol-Myers Squibb, Chugai, Eli Lilly, Genentech, Pharmacia, and Taiho Pharmaceuticals. Dr. Webster and Dr. Morris are employees of AstraZeneca.

Address for reprints: John F. R. Robertson, M.D., Department of Surgery, Nottingham City Hospital, Hucknall Road, Nottingham, NG5 1PB, UK; Fax: (011) 44(0) 115-840-2618; E-mail: john.robertson@nottingham.ac.uk.

Received January 29, 2003; revision received March 24, 2003; accepted March 24, 2003.

© 2003 American Cancer Society

DOI 10.1002/cncr.11468

anastrozole group, respectively. The incidence of joint disorders was significantly lower in the fulvestrant group ($P = 0.0036$).

CONCLUSIONS. Fulvestrant was tolerated well and was at least as effective as anastrozole in the second-line treatment of patients with ABC. This new hormonaltherapy may provide a valuable treatment option for ABC in postmenopausal women. ***Cancer*** **2003;98:229–38.** *© 2003 American Cancer Society.*

KEYWORDS: fulvestrant, estrogen receptor antagonist, duration of response, combined analysis.

The most widely used hormonal treatment for patients with breast carcinoma is the antiestrogen tamoxifen. Most patients with hormone-sensitive breast carcinoma currently receive tamoxifen at some stage during their treatment. Many of these patients eventually develop tamoxifen-resistant disease, which leaves clinicians with the problem of how best to manage patients with hormone-sensitive tumors. Other hormonal therapies include the selective aromatase inhibitors (AIs), including anastrozole and letrozole, and the steroidal agent exemestane. Both anastrozole[1,2] and letrozole[3] are effective and well tolerated. Fulvestrant (Faslodex™) is a new estrogen receptor (ER) antagonist that, unlike tamoxifen, is devoid of agonist activity.[4] Binding of fulvestrant to the ER induces a rapid loss of ER protein from breast carcinoma cells.[5] Fulvestrant down-regulates the ER in a dose dependent manner, as indicated by a dose-related reduction in the ER index.[6] Compared with tamoxifen, fulvestrant consistently reduces tumor progesterone receptor (PgR) content.[6] This novel mode of action distinguishes fulvestrant from all other antiestrogens currently in clinical use (e.g., tamoxifen, toremifene, and raloxifene).

In preclinical studies, fulvestrant was markedly more effective than tamoxifen at inhibiting the growth of human breast carcinoma cells in vitro.[7] Furthermore, fulvestrant was effective against tamoxifen-resistant breast carcinoma xenographs in an in vivo mouse model.[8] Phase I clinical trials demonstrated that a short-acting formulation of fulvestrant administered daily for 7 days before primary breast surgery was tolerated well and had antiestrogenic and antiproliferative effects,[9] whereas a Phase II study with the current long-acting formulation, which was administered once monthly, showed that fulvestrant was effective in women who had breast carcinoma that progressed after tamoxifen therapy.[10–12]

The current article reports the combined analysis of 2 Phase III clinical trials (Trial 0020 and Trial 0021), each of which compared a once-monthly intramuscular (i.m.) injection of fulvestrant 250 mg with a once-daily oral dose of the third-generation, nonsteroidal AI, anastrozole 1 mg. Both were multicenter, randomized, controlled, parallel-group trials. Each trial compared the efficacy and tolerability of fulvestrant and anastrozole in postmenopausal women with advanced breast carcinoma (ABC) who previously had disease progression after receiving endocrine treatment. The results for the individual trials have been reported previously.[13,14] Statistical plans included prospectively designed analyses of the combined data that are presented in the current report.

MATERIALS AND METHODS

Data were combined from 2 trials (Trial 0020 and Trial 0021) comparing the efficacy and tolerability of fulvestrant 250 mg given by intramuscular (i.m.) injection once monthly with anastrozole 1 mg given orally once daily. Trial 0020 was an open-label, randomized, multicenter, parallel-group trial conducted in Europe, Australia, and South Africa. Trial 0021 was a double-blind, double-dummy, randomized, multicenter, parallel-group trial conducted in North America. Recruitment for both trials occurred between May 1997 and September 1999. The full methodology for each trial has been reported previously.[13,14]

Patients

All patients were postmenopausal women with locally advanced or metastatic breast carcinoma that progressed after adjuvant endocrine therapy (primarily with tamoxifen) or after first-line endocrine therapy for advanced disease. All women had tumors with evidence of hormone sensitivity (i.e., $\geq$ 12 months of adjuvant hormonal therapy before recurrence or tumor remission or stabilization from hormonal therapy for at least 3 months before progression in patients with advanced disease or known ER or PgR positivity); a life expectancy $>$ 3 months; and, in the opinion of the investigator, were deemed appropriate candidates for subsequent hormonal therapy.

The main inclusion criteria were as follows: a World Health Organization performance status $\leq$ 2, histologic or cytologic confirmation of breast carcinoma with objective evidence of recurrence or progression of disease, and the presence of at least 1 measurable or evaluable (nonmeasurable) lesion. All

patients had to be postmenopausal (i.e., age 60 years or older, or 45 years or older age with amenorrhea for $>$ 12 months or follicle-stimulating hormone levels within postmenopausal range, or previous bilateral oophorectomy). Patients were excluded if they had received prior treatment for breast carcinoma with fulvestrant or an AI or if they had received prior extensive endocrine treatment (more than one prior endocrine treatment) for ABC. Other factors that resulted in exclusion included extensive radiation therapy within the previous 4 weeks ($\geq$ 30% of bone marrow; e.g., the whole pelvis or half of the spine) or cytotoxic treatment within the past 4 weeks, estrogen replacement therapy within 4 weeks of randomization, treatment with luteinizing hormone-releasing hormone analogs within the 3 months before randomization, or any concurrent medical illness or laboratory abnormalities that would compromise safety or prevent interpretation of results.

Bisphosphonate treatment was permitted and, although initiation of treatment during the trial was discouraged, was allowed in the absence of disease progression. Bone lesions in patients who received bisphosphonates that were initiated before or after trial entry were evaluable for progression only.

Patients in both trials were withdrawn from trial treatment at the discretion of the investigator if they had an unacceptable adverse event (AE); if noncompliance with the protocol was demonstrated; or if the patient was unwilling or unable to continue in the trial or had clinical findings (including disease progression) that conflicted with the trial protocol. All patients were monitored for progression and survival after they withdrew (unless consent was withdrawn). All patients gave written informed consent, and the relevant ethics committees approved the studies.

Trial Design

Patients were randomized to receive either fulvestrant 250 mg (1 $\times$ 5 mL on Trial 0020 or 2 $\times$ 2.5 mL on Trial 0021; n = 428) i.m. once monthly or anastrozole 1 mg (n = 423) orally once daily. Patients received the treatment to which they were randomized until there was objective evidence of disease progression or until withdrawal from the trial. The trial treatment was then stopped, standard therapy was initiated, and the patients were monitored until death.

The primary endpoint was time to progression (TTP). Secondary endpoints included the objective response (OR) rate (defined as complete response [CR] + partial response [PR] using the Union Internationale Contre le Cancer criteria),[15] duration of response (DOR), time to treatment failure (TTF), time to death (TTD), and tolerability. Clinical benefit (CB: CR + PR + stable disease [SD] $\geq$ 24 weeks) and duration of CB also were determined.

Trial Treatments

Fulvestrant was supplied as a single-dose, oily, 5% solution; and anastrozole was supplied as round, white, film-coated tablets. In Trial 0020, treatment was open label, and fulvestrant 250 mg was administered as a single, 5-mL injection into the buttocks. Because Trial 0021 was double blind, patients who received fulvestrant also received daily oral placebo tablets, and patients who received anastrozole also received monthly placebo i.m. injections. In Trial 0021, the fulvestrant dose or placebo was given as 2 2.5 mL injections, with 1 injection into each buttock.

Statistical Methods

The trials were designed to detect the superiority of fulvestrant 250 mg in terms of efficacy and tolerability compared with anastrozole 1 mg in postmenopausal women with ABC. For each trial, the final analysis was scheduled to occur when 340 events (i.e., objective disease progression or death) had occurred across the 2 groups. This would provide 90% power to detect a hazard ratio (HR) $\geq$ 1.43 or $\leq$ 0.70 for fulvestrant treatment compared with anastrozole treatment, at a significance level of 5%. To achieve the required number of events, the plan was to recruit 392 patients (196 patients in each treatment group) into each of the 2 trials. In addition to the separate analysis of each trial,[13,14] a prospective plan to undertake a combined analysis to provide more precise estimates of the treatment effects was made.

Data on the efficacy parameters were analyzed and summarized on an *intention-to-treat* basis. The protocols for these trials originally contained a fulvestrant 125 mg treatment arm. Because this dose had not been tested clinically, a preliminary summary was performed when 30 patients (across both trials) had been treated for 3 months with fulvestrant 125 mg. At that time, the lack of an OR in any patient resulted in dropping the treatment arm from the study. In addition, an interim analysis of TTP and OR was performed when 170 events had occurred in each trial. Because of this interim analysis, statistical significance levels for TTP and OR were adjusted from 5.0% to 4.86% (and confidence limits were adjusted from 95% to 95.14%). All significance levels are two-sided.

Time to progression

TTP was defined as the number of days from the date of randomization until the date of objective disease progression or until death from any cause, which ever occurred first. Death was regarded as a progression

event in patients who died prior to disease progression. For patients did not have disease progression at the time of data cut-off, data were right censored to the date of the last assessment to allow analysis.

Treatments were compared using a Cox proportional hazards regression model and included the following covariates: trial, age, performance status, measurable disease 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 using a 1% significance level was performed to determine whether there were significant treatment-by-baseline covariate interactions by considering a model that contained all treatment-by-baseline covariate interactions apart from trial. In addition, a separate test for the presence of an interaction between trial and treatment also was undertaken using a 5% significance level. Both tests were nonsignificant. A nonsignificant treatment-by-trial interaction test indicated that it was appropriate to combine the trials. Estimates of the treatment effects are expressed as HRs together with the corresponding confidence intervals (CIs) and *P* values. TTP also was summarized using Kaplan–Meier curves for each treatment group, and the median TTP was calculated.

Best objective response

Each patient was assessed for their OR at each visit to the clinic. A best OR of CR was assigned if a patient had no clinical, radiologic, or biochemical evidence of residual lesions on 1 visit with no evidence of disease recurrence or death within the subsequent 4 weeks. A best OR of PR was assigned when disease progression was not evident and disease was improved compared with the baseline assessment, with no evidence of disease recurrence or death within the subsequent 4 weeks.

The proportions of patients who had an OR were compared across the two treatments using a logistic regression model (with the same covariates that were used for TTP). A global test using a 1% significance level was performed to determine whether there were significant treatment-by-baseline covariate interactions by considering a model that contained all of the treatment-by-baseline covariate interactions apart from trial. In addition, a separate test for the presence of an interaction between trial and treatment also was undertaken using a 5% significance level. Both tests were nonsignificant, and the nonsignificant treatment-by-trial interaction test indicated that it was appropriate to combine the trials.

Fulvestrant was compared retrospectively with anastrozole for noninferiority with respect to OR and TTP using a one-sided CI of 95.57%. These limits were identical to using the upper limit of the 95.14%, two-sided CI for the analysis of TTP and the lower limit of the 95.14%, two-sided CI for the difference in response rates of OR. Based on the historic performance of anastrozole (compared with megestrol acetate) of a median TTP of approximately 5 months, the criterion for noninferiority was established by an independent group of experts who agreed that the two-sided 95% CI for the TTP HR should allow a median TTP of < 4 months for inferiority of fulvestrant to anastrozole. The requirement for showing noninferiority for TTP, therefore, was based on an upper one-sided confidence limit for the TTP HR not greater than 1.25, thus ruling out a deficiency of 25% for the experimental treatment. This criterion was used previously for United States regulatory submissions of hormonal treatments for patients with ABC. 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 $> 10\%$ (upper one-sided CI not greater than 1.10). Consequently, these criteria were used to assess the noninferiority of fulvestrant relative to anastrozole in the current trial.

Time to treatment failure

TTF was defined as the number of days from randomization until the earliest occurrence of disease progression, death from any cause, or withdrawal from treatment. For assessment purposes, data from patients who did not have treatment failure at the time of data cut-off were right censored to the last assessment date. Any patient who did not receive any trial therapy was assigned an uncensored TTF of 0 days. Statistically, TTF was analyzed using a method similar to that used to analyze TTP. The tests for treatment-by-covariate interactions were not significant, and the nonsignificant treatment-by-trial interaction test indicated that it was appropriate to combine the trials.

Duration of response

The median DOR at 22.1 months of follow-up was calculated only for patients who had an OR. DOR was defined as the number of days from randomization until the first day on which disease progression was observed. Patients who died before they reached 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 also was calculated for each group. In addition, a statistical analysis of DOR was per-

formed using all randomized patients (defined for responders as the time from onset of response to disease progression and, for nonresponders, as zero).

Duration of clinical benefit

CB was defined as the achievement of an OR or of SD $>$ 24 weeks. For patients who achieved CB, the duration of that benefit was calculated as the time between the date of randomization and the first date when disease progression was observed or when death occurred. Data for CB were summarized in the same manner as data for DOR.

Time to death

The protocol called for analyzing the TTD when $>$ 50% of patients had died. At the time of data analysis, only 35.6% of patients had died: Therefore, no formal statistical analyses were conducted for TTD.

Tolerability

All safety data were listed and summarized according to the treatment received. AEs were presented using the *Coding Symbols for Thesaurus of Adverse Reaction Terms* terminology. At the outset of the trial, seven AEs that were considered relevant to endocrine therapy were predefined for statistical analysis. These were gastrointestinal disturbances, hot flashes, vaginitis, weight gain, thromboembolic disease, urinary tract infection, and joint disorders (including arthralgia, arthrosis, and arthritis). The analysis of the predefined AEs was performed using a logistic regression analysis. Results are presented as an ORs, 95% confidence limits, and *P* values.

RESULTS

Patient Characteristics

The intention-to-treat population for the current combined analysis was 851 patients, including 428 patients in the fulvestrant 250 mg group and 423 patients in the anastrozole 1 mg group. The majority of patients (96% in the fulvestrant group and 97% in the anastrozole group) had been treated previously with tamoxifen, and a few had received megestrol acetate (0.70% in the fulvestrant group and 0.71% in the anastrozole group) and droloxifene (0.93% in the fulvestrant group only).

Characteristics of the patients in the two treatment groups are shown in Table 1. The fulvestrant-treated and anastrozole-treated groups were matched well in terms of age, weight, breast carcinoma history, prior therapy, extent of recurrent disease, and ER/PgR status. Patients in Trial 0021 were slightly heavier (fulvestrant group: mean weight, 71.2 kg; anastrozole group: mean weight, 72.7 kg) compared with patients in Trial 0020 (fulvestrant group: mean weight, 68.9 kg; anastrozole group: mean weight, 67.8 kg). Prior use of cytotoxic chemotherapy was more common among patients in Trial 0021 than among patients in Trial 0020 (63% vs. ≈ 43%, respectively), and more patients in Trial 0020 had unknown ER and PgR status (Table 2).

TABLE 1
Demographic Characteristics of Patients[a]

	Combined studies (Trials 0020 and 0021)	
	Fulvestrant 250 mg/month (n = 428)	Anastrozole 1 mg/day (n = 423)
Characteristic	**No. (%)**	**No. (%)**
Age (yrs)		
Mean	63 (—)	63 (—)
Range	33–89 (—)	33–94 (—)
Weight (kg)		
Mean	70 (—)	70 (—)
Range	37–127 (—)	40–134 (—)
Prior treatment		
Cytotoxic chemotherapy	223 (52.1)	220 (52.0)
Endocrine therapy for advanced disease	236 (55.1)	226 (53.4)
Adjuvant endocrine therapy	243 (56.8)	235 (55.6)
Hormone receptor status		
ER and/or PgR positive	342 (79.9)	352 (83.2)
ER/PgR status unknown	64 (15.0)	52 (12.3)
ER/PgR negative	22 (5.1)	19 (4.5)
Metastatic or recurrent disease at baseline		
Breast	29 (6.8)	38 (9.0)
Skin	83 (19.4)	76 (18.0)
Bone	205 (47.9)	202 (47.8)
Liver	95 (22.2)	101 (23.9)
Lung	119 (27.8)	120 (28.4)
Lymph nodes	136 (31.8)	139 (32.9)
Other	49 (11.4)	26 (6.1)
Extent of metastatic or recurrent disease at baseline		
Soft tissue only	23 (5.4)	21 (5.0)
Bone only	85 (19.9)	83 (19.6)
Visceral only	69 (16.1)	86 (20.3)
Lymph node only	37 (8.6)	38 (9.0)
Not recorded	1 (0.2)	3 (0.7)
Mixed[b]	213 (49.8)	192 (45.4)
Measurable lesions[c]	245 (57.2)	249 (58.9)
Nonmeasurable lesions	183 (42.8)	174 (41.1)

ER: estrogen receptor; PgR: progesterone receptor.

[a] Patients may have been in more than one category.

[b] Mixed was defined as breast and /or a combination of skin, bone, liver, lung, or lymph nodes.

[c] Measurable lesions were lesions that were measurable clinically in 2 perpendicular axes with at least 1 dimension that measured ≥2.5 cm or measurable using imaging in 2 perpendicular axes with at least 1 dimension that measured ≥1.0 cm.

TABLE 2
Contrasting Levels of Unknown Hormone Receptor Status between Patient Groups in the Two Trials

	Trial 0021		Trial 0020	
Unknown hormone receptor status	Fulvestrant 250 mg (n = 206) No. (%)	Anastrozole 1 mg (n = 194) No. (%)	Fulvestrant 250 mg (n = 222) No. (%)	Anastrozole 1 mg (n = 229) No. (%)
ER unknown	13 (6.3)	16 (8.2)	51 (23.0)	37 (16.2)
PgR unknown	18 (8.7)	26 (13.4)	88 (39.6)	74 (32.3)
ER and PgR unknown	13 (6.3)	15 (7.7)	51 (23.0)	37 (16.2)

ER: estrogen receptor; PgR: progesterone receptor.

TABLE 3
Progression Status throughout the Period of Treatment with Once-Monthly Intramuscular Fulvestrant (250 mg) or Once-Daily Oral Anastrozole (1 mg)

Progression status	Fulvestrant (n = 428) No. (%)	Anastrozole (n = 423) No. (%)
No disease progression	73 (17.1)	65 (15.4)
Total with disease progression	355 (82.9)	358 (84.6)
Progression during treatment	332 (77.6)	335 (79.2)
Progression after treatment withdrawal	5 (1.2)	8 (1.9)
Death before progression	18 (4.2)	15 (3.5)

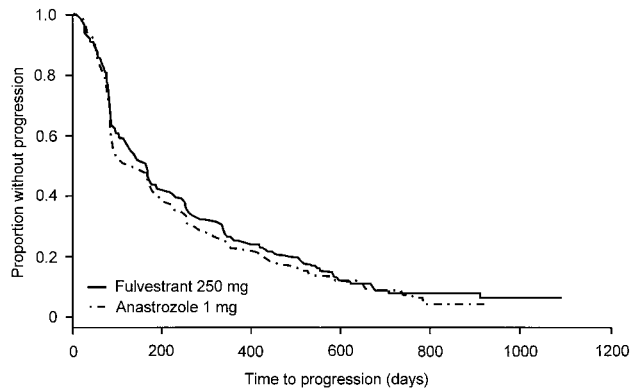

FIGURE 1. Kaplan–Meier curve of the probability of time to progression (TTP). Estimated TTP for patients receiving fulvestrant was 5.5 months, compared with 4.1 months for patients receiving anastrozole (hazard ratio, 0.95; 95% confidence interval, 0.82–1.10; $P = 0.48$).

TABLE 4
Median Time to Disease Progression for Phase III Trials 0020 and 0021 Individually and in a Prospective Combined Analysis

	TTP (mos)				
Analysis	Fulvestrant	Anastrozole	HR	CI	P value
Trial 0020	5.5	5.1	0.98	0.80–1.21	0.84
Trial 0021	5.4	3.4	0.92	0.74–1.14	0.43
Combined analysis	5.5	4.1	0.95	0.82–1.10	0.48

TTP: time to progression; HR: hazard ratio; CI: confidence interval.

Progression Status

Patients were followed for a median of 15.1 months from the date of randomization. Progression status throughout the period of treatment is shown in Table 3. At the time of analysis, 355 patients (82.9%) in the fulvestrant group and 358 patients (84.6%) in the anastrozole group had disease progression, with 17.1% and 15.4% of patients, respectively, remaining progression free: The difference between treatment groups was not statistically significant. Death occurred before tumor progression in 18 patients (4.2%) in the fulvestrant group and in 15 patients (3.5%) in the anastrozole group.

Time to Progression

The estimated median TTP was 5.5 months in the fulvestrant group, compared with 4.1 months in the anastrozole group (HR, 0.95; 95.14% CI, 0.82–1.10; $P = 0.48$). These data demonstrate noninferiority of fulvestrant relative to anastrozole for TTP. Kaplan–Meier plots of the overall TTP data are shown in Figure 1. The median TTP values for Trial 0020 and Trial 0021 individually, together with the median TTP values from the combined analysis, are shown in Table 4.

Time to Treatment Failure

The estimated median TTF was 4.6 months for fulvestrant and 3.6 months for anastrozole, although this difference was not statistically significant (HR, 0.96; 95% CI, 0.83–1.11; $P = 0.61$). The majority of treatment failures were due to objective disease progression (fulvestrant, 342 patients [93.4% of patients who failed treatment]; anastrozole, 350 patients [95.6% of patients who failed treatment]). Other reasons for treat-

TABLE 5
Best Objective Responses to Once-Monthly Intramuscular Fulvestrant (250 mg) and Once-Daily Oral Anastrozole (1 mg)

Response	Fulvestrant (n = 428) No. (%)	Anastrozole (n = 23) No. (%)
CR	20 (4.7)	11 (2.6)
PR	62 (14.5)	59 (13.9)
Total CR and PR	82 (19.2)	70 (16.5)
SD ≥ 24 wks	104 (24.3)	103 (24.3)
SD < 24 wks	6 (1.4)	4 (0.9)
No disease progression	21 (4.9)	25 (5.9)
Disease progression	215 (50.2)	221 (52.2)
Total	346 (80.8)	353 (83.5)
Clinical benefit (CR + PR + SD ≥ 24 wks)	186 (43.5)	173 (40.9)

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

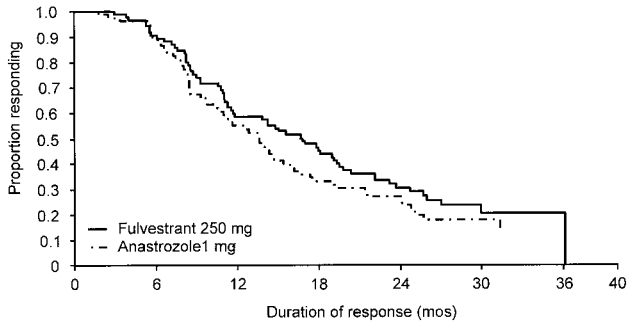

FIGURE 2. Kaplan–Meier estimates for duration of response (DOR) from randomization to disease progression in responding patients. Median DOR for patients receiving fulvestrant was 16.7 months, compared with 13.7 months for patients receiving anastrozole.

ment failure included AEs (fulvestrant, 6 patients [1.4%]; anastrozole, 5 patients [1.2%]), protocol noncompliance (fulvestrant, 6 patients [1.4%]; anastrozole, 5 patients [1.2%]), and withdrawal of informed consent (fulvestrant, 5 patients [1.2%]; anastrozole, 2 patients [0.5%]).

Objective Response Rate

The best ORs for patients in the fulvestrant and anastrozole groups are shown in Table 5. The OR rate was 19.2% for the fulvestrant group, compared with 16.5% for the anastrozole group. The difference in response rates was 2.75% (95.14% CI, 2.27–9.05%; $P = 0.31$). The lower bound of the CI for the difference in response rates was greater than −10% and therefore satisfied the criteria for the noninferiority of fulvestrant relative to anastrozole.

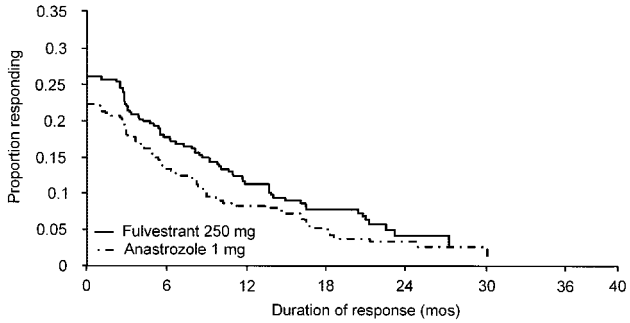

FIGURE 3. Kaplan–Meier estimates for duration of response (DOR) from the onset of response to disease progression (all patients). Ratio of average DORs (fulvestrant:anastrozole) = 1.30 (95% confidence interval, 1.13–1.50; $P < 0.01$).

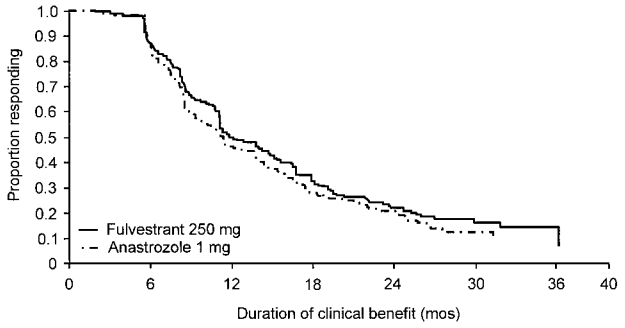

FIGURE 4. Kaplan–Meier estimates for duration of clinical benefit (DOCB). Median DOCB for patients receiving fulvestrant was 11.8 months, compared with 11.2 months for patients receiving anastrozole.

Duration of Response

Extended follow-up (median, 22.1 months) was performed to obtain more complete information for DOR. The median DOR, as measured from randomization to progression, in patients who responded to treatment was 16.7 months for the fulvestrant group ($n = 84$) and 13.7 months for the anastrozole group ($n = 73$) (Fig. 2). In the statistical analysis of DOR, which included all randomized patients, with DOR defined from the onset of response to disease progression for responders and as 0 for nonresponders, the DOR was significantly longer for patients in the fulvestrant group compared with patients in the anastrozole group. The ratio of average response durations was 1.30 (95% CI, 1.13–1.50; $P < 0.01$). Kaplan–Meier curves for DOR in all randomized patients are shown in Figure 3.

Clinical Benefit Rates

The CB rates achieved with fulvestrant and anastrozole are shown in Table 5. CB rates (CR + PR + SD ≥ 24 weeks) were 43.5% for the fulvestrant group (n

TABLE 6
Proportion of Patients with Predefined Adverse Events

Event	Fulvestrant (n = 423) No. (%)	Anastrozole (n = 423) No. (%)	P value
Gastrointestinal disturbances[a]	196 (46.3)	185 (43.7)	0.53
Hot flashes	89 (21.0)	87 (20.6)	0.91
Joint disorders	23 (5.4)	45 (10.6)	0.0036
Thromboembolic disease	15 (3.5)	17 (4.0)	0.68
Urinary tract infection	31 (7.3)	18 (4.3)	0.06
Vaginitis	11 (2.6)	8 (1.9)	0.51
Weight gain	4 (0.9)	7 (1.7)	0.35

[a] Gastrointestinal disturbances included anorexia, constipation, diarrhea, nausea, and emesis.

= 186) and 40.9% for the anastrozole group (n = 173), with the analysis showing no statistically significant difference (difference in CB rates, 2.34%; 95% CI, −4.42% to 9.36%; P = 0.51). The median duration of CB was 11.8 months for the fulvestrant group (n = 187) compared with 11.2 months for the anastrozole group (n = 174) (Fig. 4).

Time to Death

At the time of data analysis, 303 patients (35.6%) had died: 155 patients (36.2%) in the fulvestrant group and 148 patients (35.0%) in the anastrozole group. Because insufficient numbers of patients had died to permit a meaningful comparison of survival data (< 50% of patients in either the fulvestrant arm or the anastrozole arm, as specified in the trial protocol), no formal statistical analyses were conducted for TTD.

Tolerability

Both fulvestrant and anastrozole both were tolerated well. A total of 381 patients (90.1%) in the fulvestrant group and 377 patients (89.1%) in the anastrozole group reported AEs. AEs for both fulvestrant and anastrozole were predominantly mild or moderate in intensity. The most common AEs in both treatment groups, irrespective of any relation to study medication, were nausea (26.0% vs. 25.3%), asthenia (22.7% vs. 27.0%), pain (18.9% vs. 20.3%), vasodilatation (17.7% vs. 17.3%), and headache (15.4% vs. 16.8%) for the fulvestrant group and the anastrozole group, respectively. Drug-related AEs were reported by 195 patients (46.1%) in the fulvestrant group and by 171 patients (40.4%) in the anastrozole group. Withdrawals due to AEs (drug-related) were low: 2.8% (0.9%) in the fulvestrant group and 1.9% (1.2%) in the anastrozole group. Only 7 patients (1.7%) in the fulvestrant group and 5 patients (1.2%) in the anastrozole group had serious AEs that were considered at least possibly related to study medication. A total of 14 patients died as a result of an AE (8 patients in the fulvestrant group and 6 patients in the anastrozole group). Of these, only one death in the anastrozole group was considered due to a drug-related AE (cerebrovascular accident and thrombophlebitis), whereas no deaths were considered drug-related in the fulvestrant group.

Seven types of AEs were identified in the protocol for statistical analysis. The incidences of these predefined AEs for fulvestrant versus anastrozole are shown in Table 6. The only AE category with results that differed significantly between the 2 treatment groups (P = 0.0036) was joint disorders (including arthralgia, arthrosis, and arthritis), which occurred more frequently in patients who received anastrozole.

Local injection-site reactions, consisting of pain, inflammation, and hemorrhage, were mostly mild or moderate. The frequency of injection-site events was dependent on the method and volume of injection and occurred in about 1.1% of courses in patients who received the single 5-mL fulvestrant 250 mg injection (Trial 0020), 4.6% of courses in patients who received 2 × 2.5 mL fulvestrant 250 mg injections, and 4.4% of courses in patients who received 2 × 2.5 mL placebo injections (Trial 0021). Across the 2 studies, only 2 patients (0.5%) in the fulvestrant group withdrew because of an injection-site reaction.

DISCUSSION

In the current report, data were combined and analyzed from two Phase III clinical trials that investigated the efficacy and tolerability of fulvestrant compared with anastrozole in postmenopausal women who had progressed on prior endocrine treatment for ABC. Although neither study demonstrated the superiority of fulvestrant over anastrozole for TTP, a retrospective noninferiority analysis suggested that fulvestrant was at least as effective as anastrozole in the treatment of patients with ABC who had disease progression on prior endocrine therapy.

Although fulvestrant was administered differently in the 2 trials—as a single 5-mL injection in Trial 0020, compared with 2 × 2.5 mL injections in Trial 0021—previous data have demonstrated that the pharmacokinetic profiles exhibited by fulvestrant in these 2 regimens are comparable.[16] Therefore, combining the data from these two studies, which had very similar trial designs and were designed prospectively for combination, is valid. This similarity is confirmed when comparing the HRs for the median TTP from the individual studies.

The majority of patients in the trials had received, and progressed on, prior tamoxifen therapy. Fulves-

trant was effective in these patients, indicating that it differs clinically from tamoxifen and other selective ER modulators. This is in agreement with the novel mode of action established for fulvestrant.[17] To date, fulvestrant is the only ER antagonist that has demonstrated significant clinical activity in patients with tamoxifen-resistant breast carcinoma.

The primary study endpoint was TTP, and similar values were obtained for both agents, which satisfied the criterion of demonstrating the noninferiority of fulvestrant compared with anastrozole. Likewise, the secondary endpoints, TTF, OR, DOR, and duration of CB, also were similar between treatment groups. The difference in OR rates between treatment groups satisfied the criterion of demonstrating the noninferiority of fulvestrant compared with anastrozole.

In patients with late-stage ABC, a long period of response (or of SD) to treatment carries important health care cost implications by deferring or delaying the cost of managing tumor progression.[18] When all randomized patients were included in the statistical analysis of DOR, patients who were randomized to receive fulvestrant achieved a significantly longer mean DOR compared with patients who were randomized to receive anastrozole.

CB rates in the fulvestrant group were similar to the rates observed in the anastrozole group, suggesting that fulvestrant may promote patients from SD to achieving a response. Although cross-study comparisons are difficult, the OR rate achieved with fulvestrant (19%) was similar to rates reported recently for trials with other second-line therapies for patients with ABC, such as letrozole 2.5 mg (20–24%),[3,19] exemestane (15%),[20] megestrol acetate (6–16%),[1,19,20] and aminoglutethimide (12%).[3] Furthermore, the CB rate for fulvestrant in this combined analysis (44%) was similar to that reported previously for letrozole (35–36%),[3,19] exemestane (37%),[20] megestrol acetate (32–36%),[1,19,20] and aminoglutethimide (29%).[3] The OR rate for anastrozole in the current analysis (17%) was similar to previous data from Phase III trials (13%), and the CB rate (41%) also was similar to the rate reported previously (42%).[1]

The combined analysis of the tolerability data from the two trials demonstrated that fulvestrant was well tolerated, as was anastrozole. The percentage of patients who experienced an AE was similar in both treatment groups. The most common AEs in both treatment groups were nausea, asthenia, pain, vasodilatation, and headache. The majority of AEs were mild and transient in nature and did not necessitate withdrawal from therapy. The incidences of most predefined AEs (i.e., thromboembolic disease, urinary tract infection, vaginitis, and weight gain) were low on fulvestrant treatment and were comparable with the AEs observed on anastrozole. Substantial numbers of patients reported gastrointestinal disturbances; however, in most patients, the events were mild or moderate in severity and were comprised largely of nausea and emesis. It is not clear how much of this gastrointestinal toxicity was study-drug related, or may have been related to other medications patients were taking or to the disease process itself. Hot flashes, a classic estrogen withdrawal symptom, occurred in approximately one-fifth of patients, and the incidence was not significantly different between treatment groups. The greater incidence of joint disorders (i.e., arthritis, arthrosis, and arthralgia) with anastrozole, a recognized side effect of treatment with AIs,[19,21,22] was the only statistically significant difference found between treatment groups.

The incidence of injection-site reactions and withdrawals due to such reactions was low, indicating that administration of fulvestrant by injection is well tolerated and is not disadvantageous compared with oral administration. Indeed, the administration of i.m. injections may have certain benefits compared with oral therapy, because injections given by a healthcare professional ensure compliance.

Overall, these data demonstrate that fulvestrant, given as a 250-mg monthly i.m. injection, is at least as effective as daily oral anastrozole in the treatment of postmenopausal women with ABC who have been treated previously with endocrine therapy. With its proven efficacy and good tolerability profile, fulvestrant may provide a valuable new treatment option for postmenopausal women with ABC.

REFERENCES

1. Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two Phase III trials. *J Clin Oncol.* 1996;14:2000–2011.
2. Geisler J, King N, Dowsett M, et al. Influence of anastrozole (Arimidex®), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in postmenopausal women with breast cancer. *Br J Cancer.* 1996;74:1286–1291.
3. Gershanovich M, Chaudri HA, Campos D, et al. Letrozole, a new oral aromatase inhibitor: randomised trial comparing 2.5 mg daily, 0.5 mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. *Ann Oncol.* 1998;9:639–645.
4. Wakeling AE, Dukes M, Bowler J. A potent specific pure antiestrogen with clinical potential. *Cancer Res.* 1991;51:3867–3873.
5. Wakeling AE. Similarities and distinctions in the mode of action of different classes of antioestrogens. *Endocr Relat Cancer.* 2000;7:17–28.

6. Robertson JF, Nicholson RI, Bundred NJ, et al. Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfinyl)-nonyl]estra-1,3,5 (10)-triene-3,17beta-diol (Faslodex™) versus tamoxifen in postmenopausal women with primary breast cancer. *Cancer Res.* 2001;61:6739–6746.
7. DeFriend DJ, Anderson E, Bell J, et al. Effects of 4-hydroxytamoxifen and a novel pure antiestrogen (ICI 182,780) on the clonogenic growth of human breast cancer cells in vitro. *Br J Cancer.* 1994;70:204–211.
8. 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.* 1995;87:746–750.
9. DeFriend DJ, Howell A, Nicholson RI, et al. Investigation of a new pure antiestrogen (ICI 182,780) in women with primary breast cancer. *Cancer Res.* 1994;54:408–414.
10. Howell A, DeFriend D, Robertson J, Blamey R, Walton P. Response to a specific antiestrogen (ICI 182,780) in tamoxifen-resistant breast cancer. *Lancet.* 1995;345:29–30.
11. Howell A, DeFriend DJ, Robertson JF, et al. Pharmacokinetics, pharmacological, and anti-tumour effects of the specific anti-oestrogen ICI 182,780 in women with advanced breast cancer. *Br J Cancer.* 1996;74:300–308.
12. Robertson JF, Blamey RW, Howell A, Anderson L, DeFriend D, Walton P. Duration of response to ICI 182,780 appears significantly longer than "Megace" in tamoxifen-resistant breast cancer [abstract]. *Breast Cancer Res Treat.* 1996; 37(Suppl):33.
13. Howell A, Robertson JF, Quaresma Albano J, et al. Fulvestrant, formerly ICI 182,780, is as effective as anastrozole in postmenopausal women with advanced breast cancer progressing after prior endocrine treatment. *J Clin Oncol.* 2002; 20:3396–3403.
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.* 2002;20:3386–3395.
15. Hayward JL, Carbone PP, Heuson JC, Kumaoka S, Segaloff A, Rubens RD. Assessment of response to therapy in advanced breast cancer. A project of the Programme on Clinical Oncology of the International Union against Cancer, Geneva, Switzerland. *Cancer.* 1977;39:1289–1294.
16. Robertson JF. A comparison of the single-dose pharmacokinetics of ICI 182,780 ("Faslodex") 250 mg when given as either a one × 5-ml intra-muscular injection or two × 2.5-mL injections in postmenopausal women with advanced breast cancer [abstract]. *Breast Cancer Res Treat.* 2000;64:53.
17. Howell A, Osborne CK, Morris C, Wakeling AE. ICI 182,780 (Faslodex™) development of a novel "pure" antiestrogen. *Cancer.* 2000;89:817–825.
18. Brown RE, Hutton J, Burrell A. Cost effectiveness of treatment options in advanced breast cancer in the UK. *Pharmacoeconomics.* 2001;19:1091–1102.
19. Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol.* 1998;16:453–461.
20. Kaufmann M, Bajetta E, Dirix LY, et al. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer: results of a Phase III randomized double-blind trial. The Exemestane Study Group. *J Clin Oncol.* 2000;18:1399–1411.
21. Donnellan PP, Douglas SL, Cameron DA, Leonard RC. Aromatase inhibitors and arthralgia. *J Clin Oncol.* 2001;19:2767.
22. Goss PE, Winer EP, Tannock IF, Schwartz LH. Randomized Phase III trial comparing the new potent and selective third-generation aromatase inhibitor vorozole with megestrol acetate in postmenopausal advanced breast cancer patients. North American Vorozole Study Group. *J Clin Oncol.* 1999; 17:52–63.