

Comparison of Fulvestrant Versus Tamoxifen for the Treatment of Advanced Breast Cancer in Postmenopausal Women Previously Untreated With Endocrine Therapy: A Multinational, Double-Blind, Randomized Trial

Anthony Howell, John F.R. Robertson, Paul Abram, Mikhail R. Lichinitser, Richard Elledge, Emilio Bajetta, Toru Watanabe, Charles Morris, Alan Webster, Isaiah Dimery, and C. Kent Osborne

From the Christie Hospital and Holt Radium Institute, Manchester; City Hospital, Nottingham; Belvoir Park Hospital, Belfast, United Kingdom; Cancer Research Centre of Russian Academy of Medical Sciences, Moscow, Russia; Breast Center at Baylor College of Medicine and the Methodist Hospital, Houston, TX; Istituto Nazionale Tumori, Milan, Italy; National Cancer Center Hospital, Tokyo, Japan; and AstraZeneca, Wilmington, DE.

Submitted February 21, 2003; accepted February 19, 2003.

Supported by AstraZeneca Pharmaceuticals, Wilmington, DE.

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

Address reprint requests to Anthony Howell, MD, Christie Hospital National Health Service Trust, Wilmslow Rd, Manchester M20 9BX, UK; e-mail: maria.parker@christie-tr.nwest.nhs.uk.

© 2004 by American Society of Clinical Oncology

0732-183X/04/2209-1605/\$20.00

DOI: 10.1200/JCO.2004.02.112

A B S T R A C T

Purpose

To evaluate the efficacy and tolerability of fulvestrant (Faslodex; AstraZeneca Pharmaceuticals LP, Wilmington, DE), a new estrogen receptor (ER) antagonist that downregulates ER and has no agonist effects, versus tamoxifen, an antiestrogen with agonist and antagonist effects, for the treatment of advanced breast cancer in postmenopausal women.

Patients and Methods

In this multicenter, double-blind, randomized trial, patients with metastatic/locally advanced breast cancer previously untreated for advanced disease were randomly assigned to receive either fulvestrant (250 mg, via intramuscular injection, once monthly; $n = 313$) or tamoxifen (20 mg, orally, once daily; $n = 274$). Patients' tumors were positive for ER (ER+) and/or progesterone receptor (PgR+), or had an unknown receptor status.

Results

At a median follow-up of 14.5 months, there was no significant difference between fulvestrant and tamoxifen for the primary end point of time to progression (TTP; median TTP, 6.8 months and 8.3 months, respectively; hazard ratio, 1.18; 95% CI, 0.98 to 1.44; $P = .088$). In a prospectively planned subset analysis of patients with known ER+ and/or PgR+ tumors (~78%), median TTP was 8.2 months for fulvestrant and 8.3 months for tamoxifen (hazard ratio, 1.10; 95% CI, 0.89 to 1.36; $P = .39$). The objective response rate for the overall population was 31.6% with fulvestrant and 33.9% with tamoxifen, and 33.2% and 31.1%, respectively, in the known hormone receptor-positive subgroup. Both treatments were well tolerated.

Conclusion

In the overall population, between-group differences in efficacy end points favored tamoxifen, and statistical noninferiority of fulvestrant could not be demonstrated. However, in patients with hormone receptor-positive tumors, fulvestrant had similar efficacy to tamoxifen and was well tolerated.

J Clin Oncol 22:1605-1613. © 2004 by American Society of Clinical Oncology

INTRODUCTION

The selective estrogen receptor modulator tamoxifen is widely used for the first-line treatment of advanced breast cancer in both postmenopausal and premenopausal women.¹ Tamoxifen is also well established as adjuvant therapy in the early breast cancer setting,^{1,2} and has demonstrated efficacy in the prevention of breast

cancer in women at risk of developing the disease.³

Tamoxifen acts primarily by blocking the binding of estrogen to its receptor. The tamoxifen-bound receptor exhibits both estrogen agonist and antagonist properties; it has an overall response rate of approximately one-third when used as initial hormonal therapy for advanced disease in postmenopausal women.¹ However, the partial

agonist properties of tamoxifen may be responsible for some treatment failures. Tamoxifen is generally well tolerated, but may be associated with many side effects, notably gastrointestinal disturbances, hot flashes, and vaginitis. With long-term use, tamoxifen's estrogenlike properties are associated with a low, but clinically significant risk of thromboembolic events,¹ and a two- to three-fold increase in the risk of developing endometrial cancer.¹⁻³

Fulvestrant (Faslodex; AstraZeneca Pharmaceuticals LP, Wilmington, DE) is the first of a new type of estrogen receptor (ER) antagonist that downregulates the ER and is devoid of the partial agonist properties of tamoxifen when tested in laboratory models.⁴ In preclinical studies using a murine model of human breast cancer, fulvestrant had greater potency than tamoxifen at inhibiting the growth of human breast tumors, and was effective in inhibiting the growth of tumors resistant to tamoxifen.^{5,6} In postmenopausal women undergoing initial surgical resection for primary breast cancer, a single intramuscular (IM) injection of fulvestrant (50 mg, 125 mg, or 250 mg) 14 to 21 days before surgery produced a dose-dependent reduction in both ER and progesterone receptor (PgR) expression; by contrast, a single oral dose of tamoxifen (20 mg) produced an increase in PgR expression, confirming its partial agonist activity.⁷ Recently, two large (combined N = 851), multicenter, randomized trials showed fulvestrant (250 mg, once monthly via IM injection) to be at least as effective as the aromatase inhibitor anastrozole (Arimidex; AstraZeneca Pharmaceuticals LP), with a similar adverse event (AE) profile, for the treatment of postmenopausal women with hormone receptor-positive advanced breast cancer progressing on prior endocrine therapy. It was also shown to be well tolerated.^{8,9}

Here we report the first randomized trial comparing the efficacy and tolerability of fulvestrant with tamoxifen as the initial hormonal treatment of advanced breast cancer in postmenopausal women. The trial aimed to evaluate whether the absence of partial estrogenlike agonist activity of fulvestrant confers benefits over tamoxifen in this patient population.

PATIENTS AND METHODS

Study Design

This was a double-blind, randomized, parallel-group, double-dummy trial conducted at 171 centers in 26 countries. Patient recruitment took place between November 1998 and June 2000, and data cutoff was in May 2001. The trial was conducted in accordance with the Declaration of Helsinki, with the approval of an independent ethics committee at each center, and with the written informed consent of all participants.

The study population comprised postmenopausal women with metastatic or locally advanced breast cancer who had received no endocrine or cytotoxic chemotherapy for advanced disease, or had received no adjuvant endocrine therapy within 12 months before trial entry, and whose tumors were ER-positive (ER+) and/or PgR-positive (PgR+), or with ER or PgR status unknown.

During the course of the trial, an attempt was made to ascertain the ER status of some of the patients who were "ER unknown" at randomization. This resulted in a small number of patients becoming known ER-negative (ER-). Women were considered to be postmenopausal if they met any of the following criteria: age ≥ 60 years; age ≥ 45 years with amenorrhea for longer than 12 months, and an intact uterus; follicle-stimulating hormone level within postmenopausal range; or having undergone a bilateral oophorectomy. Further inclusion criteria included histologic or cytologic proof of breast cancer; objective evidence of disease recurrence or progression not considered to be amenable to curative treatment; the presence of at least one measurable lesion or nonmeasurable, evaluable lesion by Union Internationale Contre Le Cancer (UICC) criteria; WHO performance status ≤ 2 ; and life expectancy of more than 3 months.

Patients were excluded from the trial if they had life-threatening metastatic visceral disease (eg, extensive hepatic or pulmonary involvement), a history of brain or leptomeningeal involvement, or symptomatic pulmonary lymphangitic spread. Patients with discrete pulmonary parenchymal metastases were eligible provided their respiratory function was not compromised as a result of their disease. Further exclusion criteria included: previous treatment with fulvestrant; previous endocrine therapy for breast cancer, except tamoxifen as adjuvant therapy (provided treatment had stopped at least 12 months previously); treatment with luteinizing hormone-releasing hormone analogs within the previous 3 months; systemic cytotoxic therapy for advanced breast cancer or as adjuvant therapy within the previous 4 weeks (6 weeks for nitrosoureas or mitomycin C); extensive radiotherapy within the previous 4 weeks; and abnormal hepatic function.

Patients being treated with bisphosphonates were allowed to enter the trial, though their bone lesions were only assessable for disease progression. The initiation of bisphosphonate therapy during the trial was avoided if possible. If bisphosphonate treatment was initiated because of the development of new lesions or the progression of existing lesions, the patient was considered to have undergone disease progression.

Treatment Schedule

Eligible patients were allocated to treatment in balanced randomization blocks to receive either fulvestrant or tamoxifen on a 1:1 basis. The random assignment schedule was produced by the Biostatistics Group at AstraZeneca, using computer software that incorporates a standard procedure for generating random numbers. A separate random assignment schedule was produced for each center.

The fulvestrant group received fulvestrant 250 mg via IM injection (5 mL) once monthly (defined as every 28 ± 3 days), plus placebo to match tamoxifen 20 mg orally once daily. The tamoxifen group received tamoxifen 20 mg orally once daily plus placebo to match fulvestrant 250 mg via IM injection (5 mL) once monthly. Treatment started on day 1, and was required to begin within 3 days of randomization.

Trial treatment continued until there was objective evidence of disease progression, or until withdrawal from the trial due to an unacceptable AE, noncompliance with the protocol, patient lost to follow-up, or withdrawal of patient consent. Thereafter, trial treatment was stopped, and further therapy was initiated at the discretion of the investigator. All patients (unless consent was withdrawn) were followed up for progression, and thereafter for survival until death.

Efficacy and Safety Evaluations

The primary efficacy end point of the trial was the time to progression (TTP). Secondary efficacy end points included the objective response rate, clinical benefit rate, duration of response, time to treatment failure, and time to death. Quality of life and tolerability were also assessed.

Patient visits took place at screening, on day 1, and then monthly (every 28 ± 3 days). Screening assessments included medical history, ECG, chest x-ray, isotopic bone scan or skeletal survey, hematology and biochemistry assessments, tumor assessment, and WHO performance status.

Objective tumor assessments were made at each visit for the first 3 months of treatment in those patients with disease that could be assessed by physical examination, and every third month thereafter until disease progression. After progression, patients were followed up by telephone contact until death.

Tumor status was classified according to UICC criteria. The objective response rate was defined as the proportion of patients with a best overall tumor assessment of complete response or partial response, and the clinical benefit rate, as the proportion of patients with an objective response or a best overall tumor assessment of stable disease lasting ≥ 24 weeks. The TTP was defined as the period from randomization to the date of objective progression or death before objective progression. The duration of response was calculated in complete and partial responders from the date of randomization to the date of objective progression or death before objective progression. The time to treatment failure was defined as the period from randomization to the earliest occurrence of objective progression, death from any cause, or withdrawal from the trial treatment for any reason. The time to death was defined as the period from randomization until death.

Quality of life was assessed using the Functional Assessment of Cancer Therapy–Breast (FACT-B) questionnaire. The FACT-B questionnaire consists of the FACT-G (general) quality-of-life tool for cancer patients and the Breast Cancer Subscale questionnaire; both these questionnaires have been validated with respect to their psychometric properties and their sensitivity to clinical changes.^{10–12} Patients were asked to complete the FACT-B questionnaire on day 1, monthly for the first 3 months of treatment, and then every third month up to 12 months, regardless of disease progression. The measure of benefit from this instrument was the Treatment Outcome Index (TOI), which is the sum of the scores from the FACT-B subscale dimensions of physical well being, functional well being, and additional breast cancer concerns. TOI scores range from 0 (worst) to 92 (best).

Patients were monitored for clinical and laboratory toxicity at each visit, and also for 8 weeks after the last injection of fulvestrant/placebo or 30 days after the last tablet of tamoxifen/placebo, whichever was later. An AE was considered to be any detrimental change in a patient's condition during this period, unless unequivocally due to disease progression. AEs were categorized using terms based on the US Food and Drug Administration Coding Symbols for Thesaurus of Adverse Reaction Terms classification and graded according to their intensity (mild, moderate, or severe). AEs considered by the investigator to have a reasonable possibility of being caused by the trial treatment were defined as drug-related AEs.

Statistical Plan

The size of the population for the trial was based on the primary end point of TTP. Based on previous trials, the hazard ratio (HR) for TTP for tamoxifen was considered to be 0.00296 per

day (median TTP for tamoxifen, 7.7 months). To detect a hazard ratio for TTP for fulvestrant compared with tamoxifen of ≥ 1.39 or ≤ 0.72 at a significance level of 5% with 80% power, 350 end point events (objective progression or death before objective progression) were required to occur (equivalent to a change of 3 months in the median TTP for fulvestrant v tamoxifen). Based on the estimated accrual time of the trial of 15 months, and a minimum follow-up period of 8 months, this equated to 255 patients per treatment group. A trial population of at least 510 patients was therefore required.

Analyses for all efficacy end points included all randomly assigned patients and compared treatment groups on an intent-to-treat basis. A prospectively planned, secondary statistical analysis compared the efficacy end points according to ER/PgR status. Quality of life was analyzed in all patients who completed at least one FACT-B questionnaire, and toxicity in all patients who received any active trial treatment. All statistical significance levels were set at $P < .05$ and were two-sided.

All statistical analyses for determining efficacy (except time to death) were scheduled to occur after 350 end point events (objective progression or death before objective progression) had been recorded across the two treatment groups. Analysis of time to death was originally scheduled to occur when at least 50% of patients had died. However, an unscheduled survival analysis based on a cutoff date of December 31, 2002, was performed at the request of the Independent Data Monitoring Committee in March 2003. This occurred after a numerical difference in death rates was observed between groups during a routine safety follow-up.

TTP, time to treatment failure, and time to death were summarized using the Kaplan-Meier method; patients who had not experienced the event at the data cutoff date were right censored using the date of their last assessment. For these end points, the trial treatments were compared using a Cox proportional hazards model (Statistical Analysis Software [SAS] PROC PHREG; SAS Institute, Cary, NC) with baseline covariates of age, race or ethnicity, performance status, measurable compared with nonmeasurable disease, receptor status, previous adjuvant tamoxifen therapy, and use of bisphosphonate therapy for bone disease. An unadjusted analysis; ie, without covariates, was also performed for each of these end points. For the objective response rate and clinical benefit rate, the two treatments were compared using a logistic regression model (SAS PROC GENMOD; SAS Institute) with these same baseline covariates.

For the primary end point of TTP and the unscheduled survival analysis, in addition to testing for statistical significance between the two treatments, an assessment of noninferiority of fulvestrant compared with tamoxifen was made using the upper limit of the 95% CI for HR. Noninferiority was to be concluded if the upper 95% CI was ≤ 1.25 .

Quality-of-life data collected up to the date of progression was analyzed using the TOI created from the FACT-B questionnaire. The difference in TOI over time for the two treatments was compared using a generalized linear mixed model (ie, a random coefficients model) adjusted to account for both within-patient and between-patient data; the model included the same baseline covariates as for the TTP analysis plus baseline TOI. Any patient whose baseline questionnaire was completed more than 7 days after the start of treatment was excluded from the analysis.

The incidence rates of prospectively defined AEs, were formally compared by either a normal distribution or Fisher's exact test.

Table 1. Patient and Disease Characteristics at Baseline (all randomized patients)

	Fulvestrant		Tamoxifen	
	No. of Patients	%	No. of Patients	%
No. of patients	313		274	
Race or ethnicity				
White	245	78.3	223	81.4
Black	5	1.6	3	1.1
South Asian*	2	0.6	2	0.7
Hispanic	6	1.9	6	2.2
Asian†	39	12.5	28	10.2
Other (including mixed race)	16	5.1	12	4.4
Age, years				
Median	67		66	
Range	43-93		43-92	
Age distribution				
< 45 years	4	1.3	2	0.7
45-64 years	129	41.2	122	44.5
65-74 years	105	33.5	96	35.0
≥ 75 years	75	24.0	54	19.7
Weight, kg				
Median	65.1		65.0	
Range	31.4-117.3		31.0-138.8	
Tumor hormone receptor status				
ER+; PgR+	131	41.9	114	41.6
ER+/PgR-	60	19.2	45	16.4
ER+ PgR unknown	43	13.7	40	14.6
ER-/PgR+	13	4.2	13	4.7
ER-/PgR-‡	7	2.2	5	1.8
ER-/PgR unknown‡	3	1.0	3	1.1
ER unknown/PgR unknown	56	17.9	54	19.7
Total ER+ and/or PgR+	247	78.9	212	77.4
Measurable lesions present	235	75.1	208	75.9
Nonmeasurable, evaluable lesions present	219	70.0	193	70.4
Sites of measurable or evaluable disease				
Lymph node	140	44.7	122	44.5
Breast	130	41.5	113	41.2
Bone	86	27.5	89	32.5
Lung	79	25.2	67	24.5
Skin/soft tissue	69	22.0	53	19.3
Liver	30	9.6	27	9.9
Other	7	2.2	10	3.6
Previous treatment for breast cancer§				
Surgery for primary breast cancer	186	59.4	159	58.0
Adjuvant cytotoxic chemotherapy	71	22.7	66	24.1
Radiotherapy for primary breast cancer	81	25.9	80	29.2
Radiotherapy for metastatic disease	16	5.1	16	5.8
Adjuvant tamoxifen treatment	69	22.0	68	24.8

Abbreviations: ER, estrogen receptor; -, negative; +, positive; PgR progesterone receptor.

*Includes Indian subcontinent.

†Includes Far East and Japan.

‡The receptor status-negative patients were not violators because their hormone receptor status was unknown at baseline.

§Treatments previously administered in more than 2% of patients in either group.

RESULTS

A total of 587 patients were randomly assigned to treatment—313 to fulvestrant 250 mg IM every 28 ± 3 days, and 274 to tamoxifen 20 mg/d. The apparent imbalance in the number of patients randomly assigned to the two treatment groups arose purely by chance because each center randomly assigned patients to treatment by blocks of four, and

in many cases, these blocks were incomplete due to limited patient numbers at each center.

The two treatment groups were well matched at baseline with respect to race, age, weight, disease characteristics, and previous treatment history (Table 1). Approximately 40% of patients in both groups had measurable or assessable lesions in the breast at screening (Table 1). More than three-quarters of each group had tumors known to be ER+

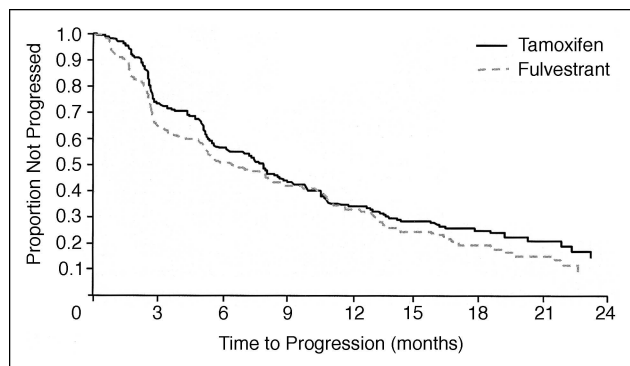


Fig 1. Kaplan-Meier plot for time to progression (all randomized patients).

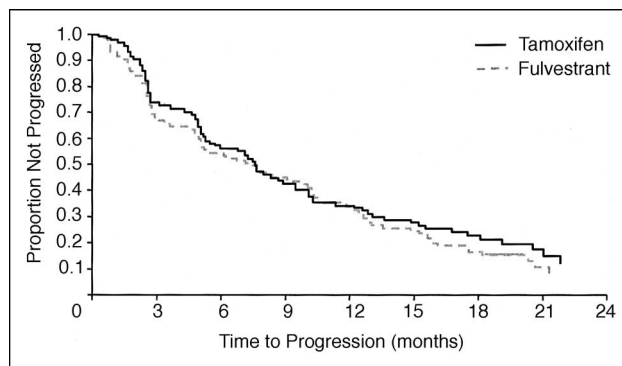


Fig 2. Kaplan-Meier plot for time to progression (patients with estrogen receptor-positive and/or progesterone receptor-positive tumors).

and/or PgR+ (78.9% with fulvestrant, 77.4% with tamoxifen). A total of 78.0% and 75.2% of patients in the fulvestrant and tamoxifen groups, respectively, received no prior adjuvant tamoxifen for their primary breast cancer.

Of the 581 patients who received trial treatment (six patients did not receive any trial treatment), 310 received fulvestrant, and 271 received tamoxifen. The median duration of trial treatment was 8.3 months for fulvestrant (range, 0.9 to 26.5 months) and 9.3 months for tamoxifen (range, 0.9 to 25.1 month). Median duration of follow-up was 14.5 months at the cutoff for efficacy and safety end points, and 31.1 months at the subsequent cutoff for survival. Data presented are for the intention-to-treat population. Similar results were obtained for the per-protocol population.

TTP

At the trial cutoff date, a total of 434 randomly assigned patients (73.9%) had experienced objective progression or died before objective progression. Kaplan-Meier curves for TTP in all randomly assigned patients are shown in Figure 1. The overall median TTP was 6.8 months in the fulvestrant group and 8.3 months in the tamoxifen group. The between-treatment difference was not significant (HR, 1.18; 95% CI, 0.98 to 1.44; $P = .088$), but the upper limit of the 95% CI (1.44) did not satisfy the predefined criterion of being ≤ 1.25 for concluding noninferiority of fulvestrant compared with tamoxifen. A similar result was obtained when the analysis of TTP was unadjusted for baseline covariates (HR, 1.15; 95% CI, 0.96 to 1.39; $P = .137$).

Analysis of patients by ER or PgR status revealed an almost identical median TTP in patients with ER+ and/or PgR+ tumors, of 8.2 months for fulvestrant and 8.3 months for tamoxifen (HR, 1.10; 95% CI, 0.89 to 1.36; $P = .39$; Fig 2).

Tumor Response to Treatment

The objective response rate in all randomly assigned patients was 31.6% in the fulvestrant group and 33.9% in the tamoxifen group, which was a nonsignificant difference (estimated treatment difference, -2.98% ; odds ratio [OR], 0.87; 95% CI, 0.61 to 1.24; $P = .45$; Table 2). The median durations

of objective response were 17.3 months and 19.8 months for fulvestrant- and tamoxifen-treated patients, respectively, with similar Kaplan-Meier curves for duration of response, as shown in Figure 3. The clinical benefit rate was 54.3% with fulvestrant and 62.0% with tamoxifen, a significant estimated treatment difference of -9.4% in favor of tamoxifen ($P = .026$).

Among patients with ER+ and/or PgR+ tumors, the objective response rate was 33.2% in the fulvestrant group and 31.1% in the tamoxifen group. Statistical analysis revealed a small, nonsignificant estimated treatment difference in favor of fulvestrant (estimated treatment difference, 2.1%; OR, 1.10; 95% CI, 0.74 to 1.63; $P = .64$). There was no significant difference in clinical benefit rate between the two treatment groups (fulvestrant, 57.1%; tamoxifen, 62.7%; estimated treatment difference, -5.65% ; OR, 0.79; 95% CI, -15.01 to 3.19; $P = .22$; Table 2).

Time to Treatment Failure

At the trial cutoff date, 248 patients (79.2%) in the fulvestrant group and 205 patients (74.8%) in the tamoxifen group had experienced treatment failure. Disease progression was the main reason for treatment failure in both the fulvestrant (91.1%) and tamoxifen (95.6%) groups; AEs accounted for only 1.6% and 1.5% of the treatment failures, respectively. There was a significant difference for time to treatment failure in favor of tamoxifen (HR, 1.24; 95% CI, 1.03 to 1.50; $P = .026$), with the median being 5.9 months for fulvestrant and 7.8 months for tamoxifen (a difference of 1.9 months). In the analysis of time to treatment failure unadjusted for baseline covariates, a similar result was obtained (HR, 1.21; 95% CI, 1.01 to 1.46; $P = .039$).

Among patients with ER+ and/or PgR+ tumors, there was no significant difference between treatments for time to treatment failure (HR, 1.15; 95% CI, 0.93 to 1.42; $P = .19$), with the median being 7.5 months with fulvestrant and 8.0 months with tamoxifen.

Survival

At the trial cutoff date for the primary analyses, only 77 patients randomly assigned to receive fulvestrant (24.6%)

Table 2. Objective Tumor Response to Treatment Overall and by Estrogen Receptor and Progesterone Receptor Status (all randomized patients)

	All Randomized Patients				Patients With EgR+ and/or PgR+ Tumors			
	Fulvestrant (n = 313)		Tamoxifen (n = 274)		Fulvestrant (n = 247)		Tamoxifen (n = 212)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Best overall response								
Complete response	30	9.6	19	6.9	22	8.9	12	5.7
Partial response	69	22.0	74	27.0	60	24.3	54	25.5
Stable disease ≥ 24 weeks	71	22.7	77	28.1	59	23.9	67	31.6
Stable disease < 24 weeks	4	1.3	1	0.4	3	1.2	1	0.5
Disease progression	131	41.9	98	35.8	95	38.5	74	34.9
Not progressed*	8	2.6	5	1.8	8	3.2	4	1.9
Objective response rate†	99	31.6	93	33.9	82	33.2	66	31.1
Objective response rate, %								
Estimated treatment difference	-2.98				2.07			
95% CI	-9.99 to 5.03				-6.00 to 11.32			
P	.45				.64			
Clinical benefit rate‡	170	54.3	170	62.0	141	57.1	133	62.7
Clinical benefit rate, %								
Estimated treatment difference	-9.43				-5.65			
95% CI	-17.96 to -1.11				-15.01 to 3.19			
P	.026				.22			

*Patients not assessable for response (other than disease progression) and had no evidence of disease progression.
†Objective response indicates a complete response or partial response.
‡Clinical benefit indicates a complete response or partial response or stable disease ≥ 24 weeks.

and 54 patients randomly assigned to receive tamoxifen (19.7%) had died. At a median extended follow-up of 31.1 months, 150 (48%) of 313 patients receiving fulvestrant and 117 (43%) of 274 receiving tamoxifen had died.

Estimated median survival was 36.9 months in the fulvestrant group and 38.7 months in the tamoxifen group. A significant difference for survival in favor of tamoxifen (HR, 1.29; 95% CI, 1.01 to 1.64; $P = .04$) was noted, based on the planned analysis with adjustments for baseline covariates. However, when the analysis was unadjusted for baseline covariates, the between group difference was not significant (HR, 1.21; 95% CI, 0.95 to 1.54; $P = .12$).

In patients with ER+ and/or PgR+ tumors, median survival in the fulvestrant group was 39.3 months compared

with 40.7 months in the tamoxifen group. This difference was not significant (HR, 1.16; 95% CI, 0.88 to 1.54; $P = .30$); nevertheless, the upper limit of the 95% CI (1.54) did not satisfy the predefined criterion of being ≤ 1.25 for concluding noninferiority of fulvestrant compared with tamoxifen.

The proportions of patients who died without 'breast cancer' recorded as the primary cause of death were 12% and 11% for fulvestrant and tamoxifen, respectively, which represents approximately a quarter of all deaths in both treatment groups.

Quality of Life

The mean TOI scores for each treatment group during the 12 months after start of treatment are presented in Figure 4. The TOI scores remained fairly constant in both groups throughout the 12-month period. Statistical analysis revealed no significant difference in TOI over time for the two treatments (estimate of difference in TOI, -0.62; 95% CI, -2.43 to 1.19; $P = .50$).

Tolerability

AEs were experienced by 269 of 310 patients who received fulvestrant (86.8%) and by 239 of 271 patients who received tamoxifen (88.2%). The most frequent AEs in both the fulvestrant and tamoxifen groups, respectively, were nausea (20.3%; 22.5%), asthenia (19.4%; 20.3%), vasodilatation (14.8%; 21.4%), pain (13.9%; 19.2%), and bone pain (13.9%; 17.0%). Most AEs were mild or moderate in severity.

A total of 129 patients in the fulvestrant group (41.6%) and 139 patients in the tamoxifen group (51.3%) experienced

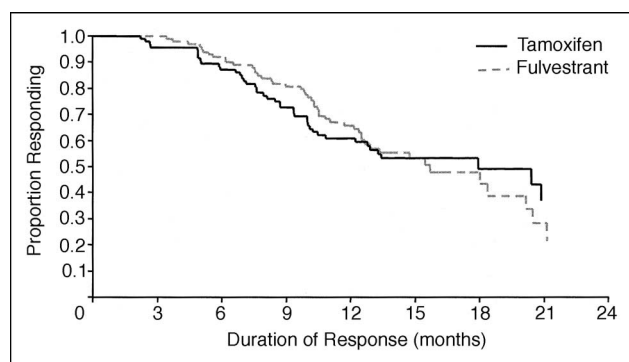


Fig 3. Kaplan-Meier plot for duration of response from randomization to progression (patients with an objective response).

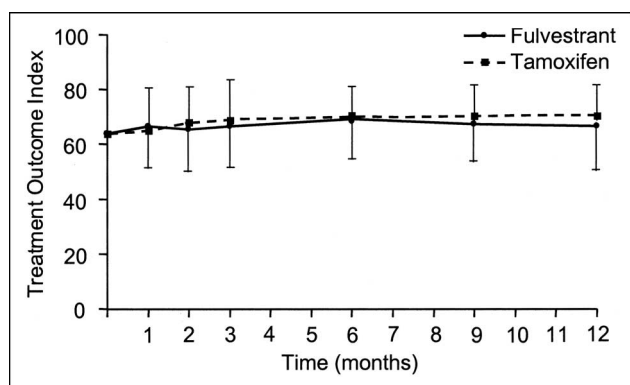


Fig 4. Mean (standard deviation [bars]) Treatment Outcome Index scores during the 12 months after the start of treatment (all patients who completed at least one Functional Assessment of Cancer Therapy–Breast questionnaire).

drug-related AEs. Table 3 presents drug-related AEs which occurred in more than 2% of patients in either treatment group. The most frequent drug-related AEs in both treatment groups were vasodilatation, injection-site pain, and nausea. Drug-related AEs led to patient withdrawal in only three patients in the fulvestrant group (cerebrovascular accident, deep vein thrombophlebitis, and pulmonary embolus, each in one patient). No AEs leading to withdrawal were adjudged to be drug-related in the tamoxifen group.

Statistical analysis of the prospectively defined AEs of gastrointestinal disturbances (nausea, vomiting, diarrhea, and constipation), hot flashes, vaginitis, and thromboembolic disease revealed no significant differences between the two treatment groups (Table 4). However, the incidence of hot flashes was lower in the fulvestrant group than in the tamoxifen group and the difference approached statistical significance (17.7% v 24.7%; $P = .0501$).

Seven patients in the fulvestrant group (2.3%) and 13 patients in the tamoxifen group (4.8%) died due to an AE. Only one of the deaths was considered by the investigator to be possibly related to trial treatment: a patient in the fulvestrant group who died of a pulmonary embolus.

DISCUSSION

This was the first randomized trial to compare the efficacy and tolerability of the new ER antagonist, fulvestrant, with tamoxifen for the treatment of postmenopausal women who have received no prior hormonal or cytotoxic therapy for advanced breast cancer. The results show fulvestrant to be active and well tolerated in this setting.

Two large randomized trials have previously shown that fulvestrant is at least as effective as anastrozole against breast cancer in postmenopausal women who failed on prior endocrine therapy.^{8,9} Anastrozole has previously demonstrated benefits over tamoxifen as first-line treatment for advanced disease,^{13,14} so it was considered probable that fulvestrant would also demonstrate benefits over tamoxifen in the first-line setting.

It was therefore unexpected that fulvestrant showed neither superiority nor noninferiority to tamoxifen for the primary efficacy end point of TTP. The almost identical median TTP for fulvestrant and tamoxifen (approximately 8 months) in the subgroup of patients with ER+ and/or PgR+ tumors (the group intended for treatment with endocrine therapies) indicates similar efficacy for the two treatments against hormone receptor–positive tumors. However, the upper 95% CI of the HR for TTP (1.36) in this subgroup does not rule out inferiority of fulvestrant compared with tamoxifen.

Table 3. Incidence of Drug-Related Adverse Events Occurring in More Than 2% of Patients in Either Treatment Group (all patients who received treatment)

	Fulvestrant (n = 310)		Tamoxifen (n = 271)	
	No. of Patients	%	No. of Patients	%
No. of patients with a drug-related adverse event	129	41.6	139	51.3
Vasodilatation	39	12.6	50	18.5
Nausea	15	4.8	23	8.5
Injection-site pain	22	7.1	22	8.1
Leukorrhea	2	0.6	14	5.2
Asthenia	13	4.2	11	4.1
Injection-site inflammation	12	3.9	5	1.8
Hyperlipidemia	3	1.0	10	3.7
Headache	11	3.5	6	2.2
Injection-site reaction	9	2.9	3	1.1
Sweating	8	2.6	7	2.6
Diarrhea	7	2.3	4	1.5
Weight gain	7	2.3	4	1.5
Vomiting	4	1.3	6	2.2
Peripheral edema	3	1.0	6	2.2

Table 4. Incidence of Prospectively Defined Adverse Events (all patients who received treatment)

	Fulvestrant (n = 310)		Tamoxifen (n = 271)		Treatment Difference (P)
	No. of Patients	%	No. of Patients	%	
Gastrointestinal disturbance*	115	37.1	117	43.2	0.16
Hot flashes	55	17.7	67	24.7	0.05
Vaginitis	12	3.9	17	6.3	0.26
Thromboembolic disease	18	5.8	9	3.3	0.22

*Nausea, vomiting, constipation, and hemorrhage.

Interestingly, an unprotocolled, exploratory analysis of TTP in patients with both ER+ and PgR+ tumors (approximately 42% of the patient population) yielded an HR of 0.85 (95% CI, 0.63 to 1.15; $P = .31$). The upper 95% CI of 1.15 is consistent with noninferiority of fulvestrant for this patient population, and the HR is suggestive of a possible benefit with fulvestrant relative to tamoxifen. Tumors expressing both ER and PgR have been shown to be most likely to respond to antiestrogen therapy.¹⁵⁻¹⁷ These findings indicate that trials involving hormonal treatments should be conducted only in patients with known hormone receptor-positive status to avoid difficulties in data interpretation and to maximize the possibility of response to treatment.

Time to treatment failure was significantly in favor of tamoxifen ($P = .026$) for the overall population, but there was no significant difference in the ER+ and/or PgR+ subgroup ($P = .19$, with a difference in medians of 0.5 months).

In an unscheduled assessment of survival in all patients, there was a significant survival benefit in favor of tamoxifen. However, in the analysis that was unadjusted for baseline covariates, there was no significant difference between the two treatment groups. As observed with the planned efficacy end points, in the prospectively defined subgroup of ER+ and/or PgR+ patients, between-group differences in death rates were small and not statistically significant. This was also the case in an exploratory analysis of survival for patients with both ER+ and PgR+ tumors (HR, 1.04; 95% CI, 0.70 to 1.56; $P = .85$).

The clinically relevant subgroup of between 22% and 25% of patients who had received prior adjuvant tamoxifen was also examined separately, however, results were found to be no different to those from the overall population.

Potential reasons for the findings of this study were considered. Firstly, there was an imbalance in the number of randomly assigned patients (39 more patients in the fulvestrant group), but this arose by chance because of some centers randomizing incomplete blocks of four patients. Despite this imbalance, the two treatment groups were well matched for baseline patient and disease characteristics. The separation in the Kaplan-Meier curves for TTP appears almost immediately and is most marked at 3 months indicating that a higher rate of early progressions occurred with

fulvestrant than tamoxifen. Pharmacokinetic studies have shown that a monthly injection of fulvestrant 250 mg takes between 3 and 6 months to produce steady-state plasma levels.¹⁸ There may similarly be a delay in time to maximal downregulation of ER, though no direct relationship between plasma levels and activity has been defined. Theoretically, this may have led to the higher early relapse rate observed with fulvestrant in this study.

Historical comparisons with other first-line trials indicate that median overall survival obtained in this trial with fulvestrant (37 v 39 months with tamoxifen, after a median follow-up of 31 months), corresponds quite closely with values obtained for letrozole (34 v 30 months with tamoxifen, after 32 months median follow-up)¹⁹ and anastrozole (39 v 40 months with tamoxifen, after 44 months median follow-up).²⁰ Neither of the first-line trials comparing an aromatase inhibitor with tamoxifen demonstrated a significant difference in survival.

The incidence of AEs prospectively identified on the basis of the expected side effects of hormonal treatments were as expected for fulvestrant and tamoxifen. Both tamoxifen and fulvestrant are associated with gastrointestinal disturbances, and in this trial, nausea was the most frequent AE in both treatment groups. Hot flashes and vaginitis result from the antiestrogenic properties of endocrine agents; in this trial, the incidence of both AEs was lower with fulvestrant than with tamoxifen, and the treatment difference in the incidence of hot flashes approached statistical significance. The lower incidence of hot flashes may be due to the relative lack of penetration into the CNS of fulvestrant as compared with tamoxifen, confirming preclinical observations with antiestrogens similar to fulvestrant.²¹ The incidence of thromboembolic events was low with both treatments. The similar number of patients in each group who died due to an event other than breast cancer confirms that there are no safety concerns with fulvestrant.

Previous randomized trials have clearly established a place for fulvestrant 250 mg/mo in the treatment of postmenopausal women with advanced breast cancer who have progressed on prior endocrine therapy, including tamoxifen. Results from this trial indicate that, in the first-line setting, differences in efficacy between the two treatment groups favored tamoxifen,

and that statistical noninferiority of fulvestrant could not be demonstrated. Nevertheless, in patients with potentially endocrine-responsive breast cancer (ER+ and/or PgR+ tumors), fulvestrant demonstrated similar efficacy to tamoxifen, with no significant difference between end points and a favorable overall tolerability profile. Results from the survival analysis were consistent with those for TTP, in that patients with both ER+ and PgR+ tumors appeared to gain most benefit from fulvestrant.

Since these drugs work by different mechanisms and are not cross-resistant, they can be used in conjunction with all other endocrine therapies to provide lengthy disease control before more toxic chemotherapy is initiated. Further clinical trials are planned to investigate whether use of a loading regimen of fulvestrant may further improve efficacy. An additional first-line trial of fulvestrant versus anastrozole is also planned.

Further investigation is required to better characterize the relative merits of fulvestrant in the first-line setting and to determine the most appropriate patient population in which fulvestrant should be used.

REFERENCES

1. Jaiyesimi IA, Buzdar AU, Decker DA, et al: Use of tamoxifen for breast cancer: Twenty-eight years later. *J Clin Oncol* 13:513-529, 1995
2. Early Breast Cancer Trialists' Collaborative Group: Tamoxifen for early breast cancer: An overview of the randomised trials. *Lancet* 351:1451-1467, 1998
3. Fisher B, Costantino JP, Wickerham DL, et al: Tamoxifen for prevention of breast cancer: Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 90:1371-1388, 1998
4. Wakeling AE, Dukes M, Bowler J: A potent specific pure antiestrogen with clinical potential. *Cancer Res* 51:3867-3873, 1991
5. Osborne CK, Jarman M, McCague R, et al: The importance of tamoxifen metabolism in tamoxifen-stimulated breast tumor growth. *Cancer Chemother Pharmacol* 34:89-95, 1994
6. Osborne CK, Coronado-Heinsohn EB, Hilsenbeck SG, et al: Comparison of the effects of a pure steroidal antiestrogen with those of tamoxifen in a model of human breast cancer. *J Natl Cancer Inst* 87:746-750, 1995
7. Robertson JF, Nicholson RI, Bundred NJ, et al: Comparison of the short-term biological effects of 7alpha-[9-(4,4,5,5,5-pentafluoropentylsulfanyl)nonyl]estra-1,3,5, (10)-triene-3,17beta-diol (Faslodex) versus tamoxifen in postmenopausal women with breast cancer. *Cancer Res* 61:6739-6746, 2001
8. Howell A, Robertson JFR, Quaresma Albano J, et al: Fulvestrant (ICI 182,780) is as effective as anastrozole in postmenopausal women with advanced breast cancer progress-

ing after prior endocrine treatment. *J Clin Oncol* 20:3396-3403, 2002

9. Osborne CK, Pippen J, Jones SE, et al: A double-blind, randomized trial comparing the efficacy and tolerability of fulvestrant with anastrozole in post-menopausal women with advanced breast cancer progressing on prior endocrine therapy: Results of a North American trial. *J Clin Oncol* 20:3386-3395, 2002

10. Cella DF, Tulsy DS, Gray G, et al: The Functional Assessment of Cancer Therapy scale: Development and validation of the general measure. *J Clin Oncol* 11:570-579, 1993

11. Hurry C, Bernhard J, Coates A, et al: Responsiveness of a single-item indicator versus a multi-item scale: Assessment of emotional well-being in an international adjuvant breast cancer trial. *Med Care* 34:234-248, 1996

12. Brady MJ, Cella DF, Mo F, et al: Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. *J Clin Oncol* 15:974-986, 1997

13. Bonnetterre J, Thürlimann B, Robertson JF, et al: Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: Results of the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability study. *J Clin Oncol* 18:3748-3757, 2000

14. Nabholz JM, Buzdar A, Pollak M: Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Results of a North American multicenter randomized trial. Arimidex Study Group. *J Clin Oncol* 18:3758-3767, 2000

15. Wittliff JL: Steroid-hormone receptors in breast cancer. *Cancer* 53:630-643, 1984

16. Jakesz R, Samonigg H, Hausmaninger H: Progesterone receptor quality and level have a significant prognostic and predictive impact in pre- and postmenopausal patients with hormone-responsive breast cancer: Six-year results of ABCSG trials 5 and 6. *Breast Cancer Res Treat* 76:45, 2002 (suppl 1, abstr 129)

17. Bardou VJ, Arpino G, Elledge RM, et al: Progesterone receptor status significantly improves outcome prediction over estrogen receptor status alone for adjuvant endocrine therapy in two large breast cancer databases. *J Clin Oncol* 21:1973-1979, 2003

18. Erikstein B, Robertson JFR, Osborne CK, et al: ICI 182,780 ('Faslodex') 250 mg monthly intramuscular (I. M.) injection shows consistent PK profile when given as either 1 x 5ml or 2 x 2.5 ml injections in postmenopausal women with advanced breast cancer (ABC). *Proc Am Soc Clin Oncol* 20:69, 2001 (abstr 2025)

19. Mouridsen H, Gershanovich M, Sun Y: Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: Analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 21:2101-2109, 2003

20. Nabholz JM, Bonnetterre J, Buzdar A: Anastrozole (Arimidex™) versus tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: Survival analysis and updated safety results. *Eur J Cancer* 39:1684-1689, 2003

21. Wakeling AE, Bowler J: Novel antiestrogens without partial agonist activity. *J Steroid Biochem* 31:645-653, 1988

Appendix

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

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Owns stock (not including shares held through a public mutual fund): Charles Morris, AstraZeneca; Alan Webster, AstraZeneca; Isaiah Dimery, AstraZeneca. Acted as a consultant within the last 2 years: Anthony Howell, AstraZeneca; Richard Elledge, AstraZeneca, C. Kent Osborne, AstraZeneca. Performed contract work within the last 2 years: John F.R. Robertson, AstraZeneca; Richard Elledge, AstraZeneca, Genentech. Received more than \$2,000 a year from a company for either of the last 2 years: Anthony Howell, AstraZeneca; John F.R. Robertson, AstraZeneca; Richard Elledge, AstraZeneca, Aventis, Genentech; Charles Morris, AstraZeneca; Alan Webster, AstraZeneca; Isaiah Dimery, AstraZeneca; C. Kent Osborne, AstraZeneca.