Anastrozole Is Superior to Tamoxifen as First-Line Therapy for Advanced Breast Cancer in Postmenopausal Women: Results of a North American Multicenter Randomized Trial

By J.M. Nabholtz, A. Buzdar, M. Pollak, W. Harwin, G. Burton, A. Mangalik, M. Steinberg, A. Webster, and M. von Euler for the Arimidex Study Group

Purpose: **The efficacy and tolerability of anastrozole (Arimidex; AstraZeneca, Wilmington, DE, and Macclesfield, United Kingdom) and tamoxifen were compared as first-line therapy for advanced breast cancer in 353 postmenopausal women.**

Patients and Methods: **The randomized, double-blind, multicenter study was designed to evaluate anastrozole 1 mg once daily relative to tamoxifen 20 mg once daily in patients with hormone receptor–positive tumors or tumors of unknown receptor status who were eligible for endocrine therapy. Primary end points were objective response (OR), defined as complete (CR) or partial (PR) response, time to progression (TTP), and tolerability.**

Results: **Anastrozole was as effective as tamoxifen in terms of OR (21% *v* 17% of patients, respectively), with clinical benefit (CR + PR + stabilization ≥ 24 weeks) observed in 59% of patients on anastrozole and 46% on tamoxifen (two-sided *P* = .0098, retrospective analysis). Anastrozole had a significant advantage over tamoxifen in terms of TTP (median TTP of 11.1 and 5.6 months for anastrozole and tamoxifen, respectively; two-sided *P* = .005). The tamoxifen:anastrozole hazards ratio was 1.44 (lower one-sided 95% confidence limit, 1.16). Both treatments were well tolerated. However, thromboembolic events and vaginal bleeding were reported in fewer patients who received anastrozole compared with those who received tamoxifen (4.1% *v* 8.2% [thromboembolic events] and 1.2% *v* 3.8% [vaginal bleeding], respectively).**

Conclusion: **Anastrozole satisfied the predefined criteria for equivalence to tamoxifen. Furthermore, we observed both a significant increase in TTP and a lower incidence of thromboembolic events and vaginal bleeding with anastrozole. These findings indicate that anastrozole should be considered as first-line therapy for postmenopausal women with advanced breast cancer.**

TAMOXIFEN HAS become the drug of choice for the endocrine treatment of advanced breast cancer in postmenopausal women who are considered likely to respond to endocrine treatment. In the adjuvant setting, tamoxifen provides significant clinical benefits in patients with early-stage breast cancer, prolonging survival[1] and reducing the incidence of new contralateral breast tumors.[2,3] Chemotherapy is also a frequently selected treatment option in patients with early-stage breast cancer, and in many cases, use of both chemotherapy and endocrine therapy has shown additive benefits.[1,4] A significant number of patients, however, still experience disease recurrence or progression during tamoxifen therapy, and, despite a good overall tolerability profile,[2,5] long-term use is associated with a two- to three-fold increase in the risk of developing endometrial cancer.[3]

The majority of breast cancers in postmenopausal women are potentially hormone-sensitive and are usually estrogen receptor–positive, requiring estrogen for proliferation.[6] The benefits of tamoxifen are thought to derive primarily from its blockade of the estrogen receptor, thus removing the stimulus to continued proliferation and resulting in regression of the tumor. However, tamoxifen is also a weak or partial estrogen agonist,[6] and therefore its use does not result in maximal suppression of the effects of estrogen.

There are alternative methods of removing the estrogen stimulus. Aromatase is a cytochrome P450-dependent enzyme that is responsible for the conversion of adrenal androgen substrates to estrogens.[7] In the postmenopausal

From the Cancer-Cross Institute, Edmonton, Alberta; Department of Oncology, Jewish General Hospital and McGill University, Montreal, Quebec, Canada; University of Texas M.D. Anderson Cancer Canter, Houston, TX; Florida Cancer Specialists, Fort Myers, FL; Louisiana State University Health Science Center, Shreveport, LA; University of New Mexico Cancer Center, Albuquerque, NM; AstraZeneca, Wilmington, DE; and AstraZeneca, Alderley Park, Macclesfield, United Kingdom.

woman, aromatase conversion of adrenal androgens provides the sole source of endogenous estrogens. A group of drugs targeted against the aromatase enzyme, the aromatase inhibitors, have been used in the treatment of breast cancer since the early 1980s.

When considering the aromatase inhibitors and tamoxifen, two randomized trials have compared tamoxifen with the first-generation aromatase inhibitor aminogluthetimide.[8,9] Response rates and other outcome parameters were identical for both agents. Other aromatase inhibitors have been compared with tamoxifen as first-line therapy. Formestane did not show any advantage over tamoxifen in this patient population, with a similar objective response (OR) rate and duration of response. However, time to progression (TTP) and time to treatment failure (TTF) were both significantly longer in the tamoxifen group.[10]

Two randomized trials have compared fadrozole with tamoxifen.[11,12] In the first of these, there were no significant differences in terms of TTF, OR rate, or survival. There was, however, a trend in favor of a longer duration of response for patients treated with tamoxifen ($P = .09$).[11] In the second study, both TTP and TTF were significantly longer in patients treated with tamoxifen when compared with patients in the fadrozole arm ($P = .01$ and .05, respectively).[12] However, in one of these studies, more clinically relevant adverse events were observed in patients receiving tamoxifen therapy.[12]

Anastrozole (Arimidex; AstraZeneca, Wilmington, DE, and Macclesfield, United Kingdom) is a new generation, selective nonsteroidal aromatase inhibitor that is administered orally as a once-daily tablet and has been available since 1995. Anastrozole has been shown to provide potent aromatase inhibition, resulting in near maximal estrogen suppression, both in the peripheral circulation and within the tumor itself.[13,14] Its use has so far been restricted to the treatment of advanced breast cancer in postmenopausal women whose disease has recurred or progressed despite treatment with tamoxifen. In these patients, anastrozole 1 mg/d was reported to significantly increase survival time and displayed a favorable toxicity profile when compared with megestrol 160 mg/d.[15] Given these data and properties of the drug, it was decided to compare the clinical effects of anastrozole and tamoxifen and to investigate whether blockade of the activity of aromatase, by preventing the production of estrogen, may induce improved safety over the partial estrogen agonist, tamoxifen. Two large, randomized, phase III trials were designed to compare the efficacy and tolerability of anastrozole and tamoxifen; both trials were designed to stand alone but also to allow for combined analysis. One trial was conducted in the United States and Canada (the North American trial) and the other in Europe, Australia, New Zealand, South America, and South Africa (the Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability [TARGET] trial).[16] These are the first studies in which these agents have been compared as first-line treatments for patients with advanced breast cancer, and this report presents the findings of the North American trial. Results of the TARGET study are also published in this issue of the *Journal of Clinical Oncology* (pp 3748-3757).

PATIENTS AND METHODS

Study Design

This was a randomized, double-blind, multicenter study conducted at 97 sites in the United States and Canada. The trial compared the efficacy and tolerability of anastrozole 1 mg once daily with tamoxifen 20 mg once daily as first-line therapy for advanced breast cancer in postmenopausal women. It was designed as an equivalence trial for efficacy and was designed to show potential safety benefits with anastrozole, for example, in endometrial and thromboembolic effects.

The primary objectives of the trial were to compare the two drugs with respect to OR rate, TTP, and tolerability. The secondary objectives were to compare treatment groups with respect to TTF, response duration, and clinical benefit duration. All patients are followed-up until objective progression and death, irrespective of treatment received.

Patient Population

All patients were required to be postmenopausal, have a diagnosis of locally advanced or metastatic breast cancer, and be suitable to receive endocrine therapy as first-line treatment for advanced disease. Postmenopausal women were defined according to one of the following criteria: women aged $\geq$ 50 years who had not menstruated during the preceding 12 months or who had castrate follicle-stimulating hormone levels ($>$ 40 IU/L), those younger than 50 years who had castrate follicle-stimulating hormone levels ($>$ 40 IU/L), or those who had undergone a bilateral oophorectomy. Prior adjuvant chemotherapy or hormonal therapy for early breast cancer was permitted, provided that no patients had received tamoxifen within 12 months before entry onto the trial.

Patients were required to have tumors that were estrogen receptor–positive and/or progesterone receptor–positive or were of unknown receptor status. Patients with tumors known to be estrogen and progesterone receptor–negative were excluded from the study. Other exclusion criteria were previous systemic therapy for advanced breast cancer, extensive visceral disease (including hepatic involvement, brain metastases, and pulmonary lymphangitic spread of tumor; serum liver enzymes could be no greater than five times the upper limit of the reference range), any concurrent medical illness or laboratory abnormalities that would compromise safety or prevent interpretation of results, or an estimated survival of less than 3 months from the start of trial therapy based on clinical judgment. At the beginning of the study, patients receiving bisphosphonates were excluded; however, because of the increasing numbers of women with advanced breast cancer being treated with bisphosphonates, the protocol was subsequently amended (at which stage 270 patients had been enrolled) and these patients could then be included. In these patients, bone metastases were considered nonassessable; however, any shrinkage of disease in the bone could not

contribute to the assignment of partial response (PR). Growth in these lesions would contribute toward an assignment of disease progression, however, and for a complete response (CR), these lesions must have disappeared.

All patients gave their written informed consent, and the appropriate institutional review board at each site approved the study.

Treatment Program

Patients were randomized to receive a daily dose of either anastrozole 1 mg once daily and tamoxifen placebo or tamoxifen 20 mg once daily and anastrozole placebo. The randomization scheme was stratified by center. Patients were instructed to take the two tablets together at approximately the same time each day. Trial treatment was continued until disease progression, at which time it was stopped. Further therapy was left at the discretion of the investigator and follow-up was performed until death.

Patients were withdrawn from active treatment because of clinically significant breast cancer progression, a serious adverse event, noncompliance with protocol procedures, or unwillingness or inability to continue the trial, or after withdrawal at the investigator's discretion. All patients who were withdrawn for reasons other than disease progression were monitored until progression was observed. After objective disease progression, patients were followed-up at 6-month intervals for survival information.

Baseline screening assessments were completed within 4 weeks before randomization. These assessments included demographic information, complete history, and clinical examination to document the sites of disease. Laboratory studies included chest x-ray, liver scan by ultrasound, computed tomography scan, or magnetic resonance imaging, bone scan, and bone survey or x-rays of areas that were found to be suggestive of abnormality on the bone scan. History of symptoms related to disease was also documented. Blood samples were collected for hematology and blood chemistry. On day 1, the date of randomization, eligible patients underwent a complete physical examination.

Efficacy Assessments

The primary efficacy measures were TTP and OR rate. The secondary efficacy measures were TTF, response duration, and clinical benefit duration. Each patient's disease was assessed clinically every 4 weeks for the first 12 weeks of treatment and then every 12 weeks until disease progression was detected. All assessments were repeated at the end of trial therapy.

Measurable disease was defined as the presence of bidimensionally or unidimensionally measurable lesions as determined by physical examination, ultrasound, or radiographic scan. Osteolytic bone lesions were considered measurable. Single metastatic lesions smaller than 0.5 cm, malignant pleural effusions or ascites, positive bone scans, and purely osteoblastic or intratrabecular bone lesions were not classified as measurable disease. Lesions not classified as measurable constituted nonmeasurable but assessable disease.

All randomized patients were assessed on the basis of International Union Against Cancer criteria for tumor response 4 weeks after the initial administration of trial medication and at all subsequent visits, up to and including the visit at which disease progression was observed. ORs were classified as CR, PR, stable disease (SD), or progressive disease for both measurable and nonmeasurable disease.[17] For a best response, patients had to have two consecutive assessments at least 4 weeks apart. The assessment criteria used were stricter than the International Union Against Cancer criteria in that patients having only nonmeasurable disease could not qualify for a PR, and a best response of SD was only assigned when responses of SD or better were observed for at least 24 weeks. If such responses had been observed for less than 24 weeks because a patient did not have measurements for 24 weeks at the time of data cutoff, then a best response of SD for less than 24 weeks was recorded. This criterion was based on data showing that a response of SD for at least 24 weeks is equivalent to CR and PR in terms of overall survival.[18-21] Responders were those patients with a best OR of CR or PR. Patients with clinical benefit were defined as those responding (CR + PR) plus those with SD for at least 24 weeks.[18-21]

TTP, TTF, duration of response, and duration of clinical benefit were calculated from the date of randomization. TTP represented the time to objective disease progression or death, whichever occurred first. TTF was the time to the earliest occurrence of progression, death, or withdrawal from randomized trial treatment. Duration of response, which was recorded for those with either a CR or PR, was the time from randomization to the time of the first observation of objective progression or death. Duration of clinical benefit in patients who achieved CR, PR, or SD for 24 weeks or more was also defined as the time from randomization to the time of the first observation of objective progression or death.

Tolerability Assessments

Adverse events were recorded on a treatment-received basis. An adverse event was defined as any detrimental change in a patient's condition after the initiation of the trial and during any follow-up period, unless considered by the investigator to be related to disease progression. Adverse events that might be expected to occur on the basis of the pharmacology of anastrozole and tamoxifen were also specifically identified (predefined events). The predefined events were depression, tumor flare, thromboembolic disease, gastrointestinal disturbance, hot flashes, vaginal dryness, lethargy, vaginal bleeding, and weight gain.

In addition to monitoring for adverse events, routine laboratory tests were performed at baseline, at selected times during therapy, and at withdrawal or study end. The results of clinical laboratory tests were reviewed for clinically relevant changes. Physical examinations were performed and body weight, blood pressure, and pulse rate were recorded at baseline, at selected times during therapy, and at study end or withdrawal.

Statistical Analysis

The trial was designed to compare anastrozole with tamoxifen, using TTP and OR rate as the two primary efficacy end points, and was powered to demonstrate equivalence, as defined by the 95% one-sided confidence interval, in each of these end points. For TTP, the comparison between anastrozole and tamoxifen was expressed in terms of the hazards ratio (tamoxifen:anastrozole), which estimates the chance of progression on tamoxifen in a given time period in relation to the chance of progression on anastrozole in the same time period. A hazards ratio of more than 1 indicates a superiority for anastrozole. The prespecified criterion for equivalence would be met if the lower one-sided 95% confidence limit for the hazards ratio was ≥ 0.80; ie, equivalence would be concluded if a 20% or greater advantage for tamoxifen could be ruled out with 95% confidence.

For response rate (CR + PR), the comparison between treatments was expressed in terms of the difference in response rates (anastrozole − tamoxifen). A difference greater than zero would indicate a higher response rate for anastrozole, whereas a difference less than zero would indicate a higher response rate for tamoxifen. The prespecified

criterion for equivalence in response rates would be met if the lower one-sided 95% confidence limit for the difference in response rates was $\geq -10\%$; ie, equivalence would be concluded if a difference in response rates of 10% or more in favor of tamoxifen could be ruled out with 95% confidence.

The Cox proportional hazards regression model was used to assess treatment equivalence for TTP and TTF. The OR rate was compared between the treatment groups using logistic regression. All efficacy analyses were performed on an intention-to-treat basis and were adjusted for the covariates of age, previous endocrine therapy (yes or no), extent of disease at entry, and hormonal receptor status.

In addition to the prospectively identified statistical analyses that were designed to demonstrate equivalence, further analyses assessed whether anastrozole showed any benefit over tamoxifen for TTP. Duration of response was measured only for responding patients from the date of randomization to the date of first observed progression or death from any cause. Duration of response and duration of clinical benefit were summarized for each treatment group using the Kaplan-Meier method, with no formal statistical comparisons performed.

RESULTS

At the time of analysis, the median duration of follow-up was 17.7 months and disease progression had been observed in 71% of patients.

Patient Characteristics

Recruitment into this study began on February 26, 1996, and stopped on July 9, 1998, when the prespecified number of patients had been randomized in the TARGET trial,[16] which had the same protocol and objectives. The decision to stop recruitment was made before any analysis of either study. At this time, 353 patients from 97 centers in North America and Canada were entered onto the study and randomized to one of the two treatment groups (anastrozole 1 mg, n = 171; tamoxifen 20 mg, n = 182). The groups formed by randomization were well balanced with respect to demographic and pretreatment characteristics (Table 1).

Tumor Response

A total of 21% of patients in the anastrozole group and 17% in the tamoxifen group achieved CR or PR (Table 2). The estimated difference in OR rates between anastrozole and tamoxifen after adjustment for patient characteristics was 5.0% (lower 95% confidence limit, −1.9%). The equivalence criterion for the OR rate was that the lower one-sided 95% confidence limit for the difference in response rates could not be less than −10%.

In the anastrozole group, 59% of patients gained clinical benefit (CR + PR + SD = 24 weeks) from therapy, compared with only 46% of patients in the tamoxifen group. Statistical comparisons between treatment groups were not planned for clinical benefit rates. However, the observed clinical benefit rates seen in this trial prompted a retrospective statistical comparison of treatment groups. This analysis indicated that the difference between treatment groups was statistically significant ($P = .0098$). Because this was a posthoc statistical comparison, this result should be treated with care.

Table 1. Demographic and Pretreatment Characteristics

Characteristic	Anastrozole 1 mg (n = 171)		Tamoxifen 20 mg (n = 182)	
	No. of Patients	%	No. of Patients	%
Age, years				
Median	68		67	
Range	30-88		40-92	
Weight,* kg				
Median	72		69	
Range	43-121		36-140	
Breast cancer disease status at first diagnosis				
Advanced	52	30.4	60	33.0
Early	118	69.0	122	67.0
Unknown	1	0.6	0	0
Prior adjuvant treatment				
Hormonal only	21	12.3	20	11.0
Cytotoxic only	32	18.7	37	20.3
Both	15	8.8	13	7.1
None	102	59.6	111	61.0
Unknown	1	0.6	1	0.5
Receptor status				
ER+, PgR+	109	63.7	121	66.5
ER+, PgR−	32	18.7	31	17.0
ER+, PgR unknown	4	2.3	4	2.2
ER−, PgR+	6	3.5	5	2.7
ER−, PgR−	1	0.6	0	0
ER unknown, PgR+	0	0	1	0.5
Unknown	19	11.1	20	11.0
Sites of metastatic disease†				
Soft tissue	86	50.3	91	50.0
Skin	52	30.4	50	27.5
Lymph	63	36.8	64	35.2
Bone	112	65.5	98	53.8
Visceral	83	48.5	87	47.8
Lung	76	44.4	68	37.4
Liver	13	7.6	30	16.5
Intra-abdominal	7	4.1	8	4.4
Other	0	0.0	1	0.5
No assessable disease	2	1.2	2	1.1
Extent of metastatic disease				
Soft tissue only	18	10.5	33	18.1
Bone only	46	26.9	42	23.1
Bone and soft tissue only	22	12.9	18	9.9
Visceral disease with no liver involvement	70	40.9	57	31.3
Visceral disease with liver involvement	13	7.6	30	16.5
No assessable disease	2	1.2	2	1.1
Measurable disease	117	68.4	140	76.9
No measurable disease	54	31.6	42	23.1

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

*Weight was recorded for 168 patients in the anastrozole group and 178 patients in the tamoxifen group.

†Patients may be in more than one category; No assessable disease = 4 patients with nonmetastatic disease.

Table 2. Objective Tumor Response Rates in Patients Treated With Anastrozole or Tamoxifen

	Anastrozole 1 mg (n = 171) (%)	Tamoxifen 20 mg (n = 182) (%)
Best OR, CR + PR*	21.1	17.0
Clinical benefit, CR + PR + SD ≥ 24 weeks	59.1†	45.6
CR	2.9	2.7
PR	18.1	14.3
SD ≥ 24 weeks	38.0	28.6
SD < 24 weeks	4.1	2.2
Progression	36.8	52.2

*Median duration of response (CR + PR) was 16.1 months (range, 2.1 to 30.1 months) in the anastrozole group and 17.9 months (range, 2.8 to 30.4 months) in the tamoxifen group.

†P = .0098 (anastrozole *v* tamoxifen).

The median duration of clinical benefit from the time of randomization was 16.5 months (range, 2.1 to 30.1 months) and 14.5 months (range, 2.5 to 30.4 months) for patients receiving anastrozole and tamoxifen, respectively. The median duration of response, as calculated from the date of randomization to the time of the first observation of objective progression or death, was similar for both groups: 16.1 months (range, 2.1 to 30.1 months) for anastrozole and 17.9 months (range, 2.8 to 30.4 months) for tamoxifen.

TTP

The median TTP was 11.1 months for patients in the anastrozole group and 5.6 months for patients in the tamoxifen group. The estimated progression hazards ratio for tamoxifen 20 mg versus anastrozole 1 mg after adjustment for patient characteristics was 1.44 (lower 95% confidence limit, 1.16), showing that anastrozole is at least as effective as tamoxifen; to achieve equivalence, the lower one-sided 95% confidence limit for the hazards ratio had to be ≥ 0.80. A Kaplan-Meier plot of TTP is presented in Fig 1. Additional analysis of the TTP data indicated that the advantage seen with anastrozole was statistically significant at a value of P = .005.

TTF

Treatment failure occurred in 135 (79%) of 171 patients randomized to anastrozole and 152 (84%) of 182 patients randomized to tamoxifen. Disease progression was the main reason for treatment failure in both treatment groups (116 [67.8%] of 171 patients receiving anastrozole and 137 [75.3%] of 182 patients receiving tamoxifen). The number of patients who experienced treatment failure because of adverse events was 4.7% for anastrozole and 3.3% for tamoxifen.

Anastrozole was at least as effective as tamoxifen in terms of TTF; Fig 2 shows the Kaplan-Meier plot of TTF. The estimated TTF hazards ratio for tamoxifen 20 mg versus anastrozole 1 mg was 1.35 (lower 95% confidence limit, 1.11), once again showing that anastrozole was at least as effective as tamoxifen.

Survival

At the time of analysis, 28.3% of patients had died. Analysis of survival was not made at this time, because the data were considered to be immature. An analysis based on these data may therefore be potentially misleading. Per protocol analyses of the efficacy end points, excluding patients with major departures from the protocol but using the same methods of analysis provided similar results to those of the ITT analyses.

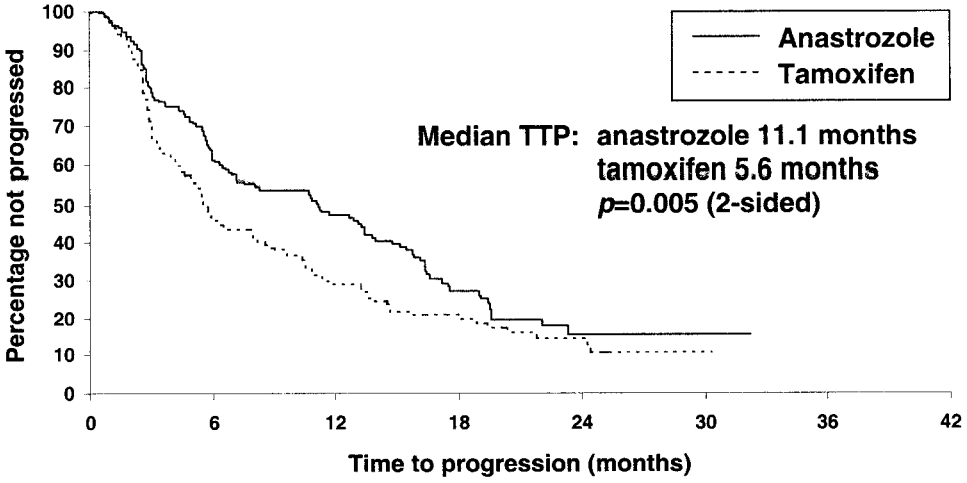

Fig 1. Kaplan-Meier probability of TTP in patients receiving anastrozole 1 mg or tamoxifen 20 mg once daily.

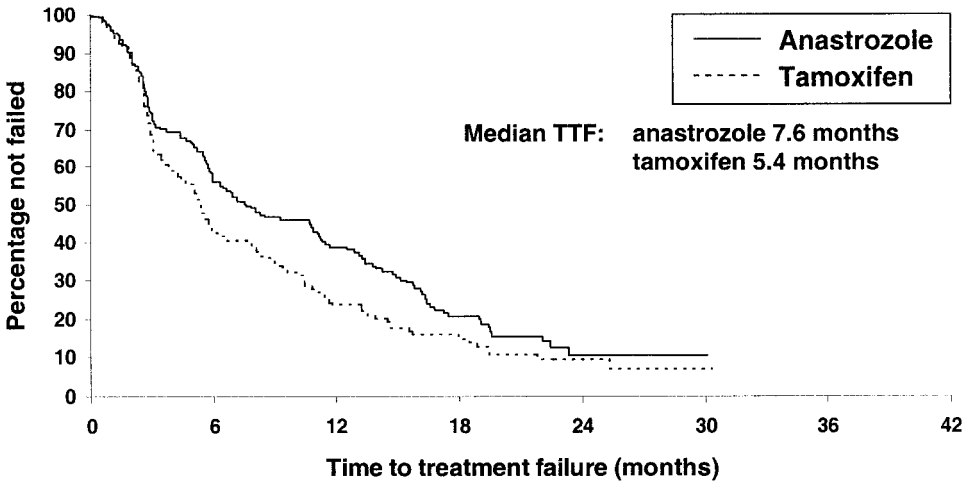

Fig 2. Kaplan-Meier probability of the TTF in patients receiving anastrozole 1 mg or tamoxifen 20 mg once daily.

Tolerability

Anastrozole and tamoxifen were both well tolerated in the majority of patients. The five most frequently reported adverse events in both groups are listed in Table 3. In total, 17 (4.8%) of 352 patients had an adverse event that led to withdrawal from the study. Of these, nine (5.3%) of 170 patients were in the anastrozole group and eight of 182 patients (4.4%) were in the tamoxifen group. However, the adverse events were considered to be drug-related in only eight of the 17 patients (three [1.8%] of 170 patients in the anastrozole group and five [2.7%] of 182 patients in the tamoxifen group).

Table 4 shows the incidences of predefined adverse events. Numerical differences were observed between the treatment arms, with fewer thromboembolic events and vaginal bleeding among patients in the anastrozole arm compared with patients in the tamoxifen arm.

There were four deaths during the treatment period of this study (three in the anastrozole group and one in the tamoxifen group) which were not considered to be related to breast cancer. None were related to study treatment. Deaths that occurred among patients receiving anastrozole were caused by gastrointestinal hemorrhage, dyspnea, and suicide; the death that occurred in a patient receiving tamoxifen was caused by angioedema.

Table 3. Most Frequently Reported Adverse Events in the Anastrozole and Tamoxifen Groups

	Anastrozole 1 mg (n = 170)		Tamoxifen 20 mg (n = 182)	
	No. of Patients*	%	No. of Patients*	%
Hot flashes	62	36.5	44	24.2
Asthenia	54	31.8	65	35.7
Nausea	52	30.6	62	34.1
Pain	43	25.3	48	26.4
Back pain	41	24.1	43	23.6

*Number of patients reporting incidences.

DISCUSSION

This study is one of two randomized multicenter trials, identical in design and objectives, to first report on the comparative efficacy of tamoxifen and anastrozole as first-line endocrine therapy for postmenopausal patients with advanced breast cancer. The efficacy results are particularly

Table 4. Incidence of Predefined Adverse Events, Irrespective of Causality, Reported in Each Treatment Group

	Anastrozole 1 mg (n = 170)		Tamoxifen 20 mg (n = 182)	
Adverse Event Category	No. of Patients*	%	No. of Patients*	%
Depression	9	5.3	14	7.7
Tumor flare	7	4.1	10	5.5
Thromboembolic disease	7	4.1	15	8.2
Venous thromboembolism	2	1.2	4	2.2
Coronary thrombosis	1	0.6	4	2.2
Cerebral thrombosis	3	1.8	3	1.6
Gastrointestinal disturbance	91	53.5	104	57.1
Nausea	52	30.6	62	34.1
Vomiting	25	14.7	22	12.1
Diarrhea	29	17.1	23	12.6
Hot flashes†	65	38.2	50	27.5
Vaginal dryness	8	4.7	7	3.8
Vaginal bleeding	2	1.2	7	3.8
Lethargy	2	1.2	6	3.3
Weight gain	5	2.9	2	1.1

*Number of patients reporting incidences.

†In this table, hot flashes includes the adverse events for hot flashes and sweating.

important, as they show that in this patient population anastrozole is at least as effective as tamoxifen. Furthermore, an additional analysis indicates superiority for anastrozole compared with tamoxifen in terms of TTP (P = .005).

Although the OR rate was not statistically different between the two treatment arms, this study shows that a significantly greater number of patients receiving anastrozole achieve clinical benefit (CR + PR + SD $\geq$ 24 weeks) compared with those receiving tamoxifen (respectively, 59% *v* 46%, P = .0098, retrospective analysis). This result is of particular note because several studies have reported SD $\geq$ 24 weeks as having the same clinical value as CR or PR for breast cancer patients treated with endocrine therapy. This fact has led to the concept of clinical benefit, which is nowadays widely accepted as a valuable clinical end point for assessing the efficacy of endocrine therapy in advanced breast cancer.[15,18-21]

With a hazards ratio of 1.44 and a lower 95% confidence limit of 1.16, the TTP results show that patients who received tamoxifen were 44% more likely to experience disease progression in a given period of time than those who received anastrozole, with superiority in favor of anastrozole in the additional analysis (P = .005). These results are reflected by the median TTP, which is doubled with anastrozole as compared with tamoxifen (11.1 *v* 5.6 months, respectively). The TTP with tamoxifen observed in this trial seems shorter than previously reported in other trials of first-line endocrine therapy for advanced breast cancer[10-12,22]; however, it is similar to that reported in a recently conducted trial of tamoxifen versus toremifene.[22]

In our trial, patient characteristics were well balanced. Although there were more visceral liver metastases among patients in the tamoxifen group, there was also more soft-tissue disease. The majority of patients had bone or visceral metastases. The incidence of visceral metastases was high for a first-line endocrine therapy study (approximately 48% for both arms). There was a slight imbalance in liver metastases (tamoxifen, 30 patients [16.5%] *v* anastrozole, 13 patients [7.6%]); however, it should be noted that patients with extensive liver metastases were excluded from the trial, and there was no difference between tamoxifen and anastrozole when all types of visceral disease were considered. The statistical analysis was also adjusted for the site of disease at entry. In a large systematic review of published randomized trials of systemic therapy in advanced disease recently reported by Fossati et al,[23] the incidence of visceral metastases was found to be 35% in 35 trials involving 5,160 patients that compared tamoxifen with other endocrine agents. The incidence of visceral metastases is higher in this trial than that normally observed in the patient population involved in endocrine trials in metastatic disease as reported by Fossati et al. This may contribute to the short TTP observed with tamoxifen.

Previous exposure to endocrine therapy in the adjuvant setting has also been claimed to be a parameter potentially influencing outcome in the advanced setting. In this study, this factor was well balanced between the two arms and was present in only 21% of patients treated with anastrozole and 18% of those treated with tamoxifen, and patients must have had a least a 12-month drug-free period after adjuvant tamoxifen to be entered onto the study.

It is established that the benefits of endocrine therapy are greatest in women whose tumors are hormone receptor–positive, whereas the effect of endocrine therapy is questionable in patients with negative hormone receptor status.[1,5,6] Our patient population seems homogeneous, with 89% of patients with hormonal receptor–positive tumors and only 11% with tumors of unknown hormone receptor status (a proportion of which might be hormone receptor–negative). This factor is of primary importance for the appropriate assessment of endocrine therapies in breast cancer. The low percentage of patients with tumors of unknown receptor status observed in this trial provides optimum conditions to assess the differential clinical value of anastrozole and tamoxifen and suggests that anastrozole is superior to tamoxifen in patients who are known to have hormone receptor–positive breast cancer.

No hormonal agent has previously been shown to be more efficacious than tamoxifen for the first-line therapy of metastatic breast cancer. Tamoxifen has been compared with megestrol acetate,[24-29] medroxyprogesterone acetate,[30-32] and various other antiestrogenic manipulations, including diethylbestrol,[33,34] androgens,[35] fluoxymesterone,[36] and new antiestrogens,[22,37] in phase III randomized trials. In all cases, responses and outcome parameters were not significantly different between tamoxifen and these agents.[23] However, in the majority of cases, the toxicity profile was more favorable with tamoxifen. This led to the sequential endocrine strategy, classically based on toxicity profiles rather than proven efficacy benefits, firmly establishing tamoxifen as the first-line endocrine agent for breast cancer.

When considering the data from this trial and from the recent fadrozole and formestane studies,[10-12] anastrozole is the only aromatase inhibitor that has been shown to be at least as effective as tamoxifen in terms of TTP, with formestane and fadrozole being inferior to tamoxifen for these end points. The significantly longer TTP observed in the present study is, as far as we are aware, the first time an endocrine agent has shown superior efficacy to tamoxifen in large trials in the advanced breast cancer setting.

Overall, adverse events were seen at a similar incidence in both the anastrozole and tamoxifen groups in this study. The type and distribution of adverse events was relatively comparable to those found in other studies of anastrozole or tamoxifen[5,38] and are considered, for the most part, to be characteristic of the patient population of postmenopausal women with advanced breast cancer. Previous studies of the new-generation aromatase inhibitors fadrozole, vorozole, letrozole, and anastrozole have indicated that nausea, vomiting, and diarrhea are probably a class effect of these agents.[15,39,40] However, in contrast to these studies and the review by Fossati et al,[23] in which gastrointestinal side effects seemed to be more frequent with aromatase inhibitors compared with other endocrine agents, a comparable incidence of gastrointestinal disturbances between the two treatment groups was observed in this trial (anastrozole, 53.5%; tamoxifen, 57.1%).

Adverse events associated with endocrine agents frequently result from their antiestrogenic properties, including, in particular, hot flashes and vaginal dryness.[5,38] In this study, hot flashes were slightly more frequent with anastrozole, whereas vaginal dryness was reported at a similar incidence in both the tamoxifen and anastrozole treatment groups. In addition, more patients in the tamoxifen group reported vaginal bleeding compared with those in the anastrozole group (3.8% *v* 1.2%, respectively), perhaps providing indirect evidence of lack of stimulatory effect of anastrozole on the endometrium.[41]

Thromboembolic events have been reported with tamoxifen.[2,3,5,12] In our study, a lower incidence of thromboembolic diseases (venous and arterial) was observed in anastrozole-treated patients compared with tamoxifen-treated patients (4.1% *v* 8.2%, respectively). No increase in the incidence of serious cardiovascular events was seen in patients treated with anastrozole. These results suggest that the incidence of thromboembolic events with anastrozole may be similar to that which might be seen with placebo.

In conclusion, the results of this study confirm that anastrozole is at least as effective as tamoxifen for the first-line treatment of advanced breast cancer in postmenopausal women and demonstrates a statistically significant improvement in TTP ($P = .005$) and clinical benefit ($P = .0098$, retrospective analysis). This is the first observation in large randomized trials of an endocrine agent showing a significant efficacy benefit over the current treatment of choice, tamoxifen, when used as first-line treatment for advanced breast cancer. Both treatments were similarly well tolerated. However, fewer incidences of thromboembolic events and vaginal bleeding were reported in patients treated with anastrozole.

These data provide further insight into the potential role anastrozole may play in early breast cancer. The Arimidex or Tamoxifen Alone or in Combination (ATAC) Trial, comprising more than 9,000 patients, is expected to report on this in the next 2 years, and the results are eagerly awaited. For now, data from the North American first-line trial confirm that anastrozole has a favorable efficacy-toxicity ratio and thus should now be considered for use as first-line therapy for postmenopausal women with advanced breast cancer.

APPENDIX

The Arimidex Study Group includes the following investigators: Rafat H. Ansari, MD, FACP, Michiana Hematology-Oncology, PC, South Bend, IN; Andrew Arnold, MD, Hamilton Regional Cancer Centre, Hamilton; Susan Dent, MD, Ontario Cancer Treatment and Research Foundation, Thunder Bay Regional Cancer Centre, Thunder Bay; Robert Myers, MD, Credit Valley Professional Bldg., Mississauga; Eva Tomiak, MD, Ottawa Regional Cancer Centre, Ottawa Civic Division, and Shailendra Verma, MD, Ottawa Regional Cancer Centre, Ottawa General Hospital Division, Ottawa; Maureen Trudeau, MD, Women's College Hospital, Department of Oncology, Toronto; Labib Zibdawi, MD, Community Cancer Clinic, York County Hospital, Newmarket, Ontario; David Bowman, MD, Manitoba Cancer Treatment and Research Foundation, Winnipeg, Manitoba; Pradip Ganguly, MD, Department of Radiation Oncology, H. Bliss Murphy Cancer Centre, St. John's, Newfoundland; David Holland, MD, Lethbridge Cancer Clinic, Lethbridge, Alberta; Paul Klimo, MD, Department of Oncology, Lion's Gate Oncology Clinic, North Vancouver, British Columbia; Jean Latreille, MD, Division of Hematology & Medical Oncology, Montreal; Jean Robert, MD, FRCSC, CHA Pavillon St-Sacrement, Quebec City, Quebec; and Maria Rosalia B. Tria Tirona, MD, Allan Blair Cancer Centre, Pasqua Hospital, Saskatchewan, Canada; Rita A. Blanchard, MD, Boston Medical Center; Steven E. Come, MD, Beth Israel Deaconess Medical Center, Boston; Kala Seetharamen, MD, Saint Vincent Hospital, Worcester; and Charles F. White, MD, Lahey Clinic Medical Center, Department of Medical Oncology, Burlington, MA; Peter Bushunow, MD, Department of Pharmacy, Rochester General Hospital; Timothy J. Woodlock, MD, St Mary's Hospital, Rochester; Ellis Levine, MD, Roswell Park Cancer Center, Buffalo; Stefan Madajewicz, MD, Medical Oncology HSCT-17, Stony Brook; Harish K. Malhotra, MD, FACIP, FACP, North Shore Hematology/Oncology Associates, PC, East Setauket; and Heidi Puc, MD, Hematology/Oncology Associates, Syracuse, NY; Peter D. Byeff, MD, Hematology/Oncology, Southington; and Ivan S. Lowenthal, MD, Northwestern Connecticut Oncology and Hematology Associates, Torrington, CT; Ray H. Clark, MD, Hematology/Oncology Associates, Jackson; Nikolay V. Dimitrov, MD, Professor of Medicine, Department of Medicine, Michigan State University, East Lansing; Providence Cancer Center, Southfield; and Eric P. Lester, MD, Lakeland Medical Center, St Joseph, MI; Gary I. Cohen, MD, Greater Baltimore Medical Center; Myo Thant, MD, PA, Franklin Square Hospital; and Katherine

APPENDIX (Cont'd)

Tkaczuk, MD, University of Maryland Cancer Center, Baltimore, MD; H. Peter DeGreen, MD, Lancaster Cancer Center, Ltd, Lancaster; Richard Kosierowski, MD, North Penn Hospital, Lansdale; Barry C. Lembersky, MD, Allegheny General Hospital, Pittsburgh; Edward T. O'Brien, MD, The Regional Cancer Center, Erie; Peter V. Pickens, MD, Abington Hematology Oncology Associates, Inc., Meadowbrook; and Mary A. Simmonds, MD, FACP, Central PA Hematology & Medical Oncology Associates, Lemoyne, PA; Margaret A. Deutsch, MD, Raleigh Internal Medicine, Raleigh; and Lyndsay Harris, MD, Duke University Medical Center, Durham, NC; Robert O. Dillman, MD, Hoag Cancer Center, Newport Beach; Fred Kass, MD, Cancer Foundation of Santa Barbara, Santa Barbara; L. Wayne Keiser, MD, Redwood Regional Medical Group, Santa Rosa; Debasish Tripathy, MD, University of California at San Francisco Cancer Center, Breast Care Center, San Francisco; and Sharon J. Yee, MD, Arcadia, CA; William R. Edwards, MD, Rockford Clinic, Rockford; Karen Hoelzer, MD, Springfield Clinic, St John's Pavilion, Springfield; Gershon Y. Locker, MD, The Evanston Hospital, Kellogg Cancer Care Center, Evanston; Samuel G. Taylor, MD, Creticos Cancer Center, Chicago; and Janet Wolter, MD, Rush-Presbyterian-St. Luke's Medical Center, Chicago, IL; Michael Entmacher, MD, Fox Chase Cancer Center, Memorial Hospital of Burlington County, Mt Holly; and Judie R. Goodman, DO, and Generosa Grana, MD, Cooper Cancer Institute, Voorhees, NJ; Frederick Ey, MD, HealthFirst Medical Group, Portland; Nagendra Tirumali, MD, Hematology/Oncology, Kaiser Permanente, Portland; Robert Granatir, MD, Office of Drs Granatir & Jacquin, Salem; and Richard H. Woods, MD, Bend Memorial Clinic, Bend, OR; M. Francisco Gonzalez, MD, Center for Cancer Treatment and Research, Columbia; and Rayna Kneuper-Hall, MD, Medical University of South Carolina, Charleston, SC; Allan M. Grossman, MD, Knoxville Hematology & Oncology Associates, Knoxville; and Larry Schlabach, MD, University Oncology Associates, Chattanooga, TN; C. Eric Hartz, MD, Cancer Care of Maine, Bangor, ME; David L Headley, DO, The Oncology Clinic, PC, Colorado Springs, CO; Robert Hirsch, MD, Comprehensive Cancer Research Group, Inc, Comprehensive Cancer Center, North Miami Beach; John Horton, MB, ChB, H. Lee Moffitt Cancer Center & Research Institute, Tampa; Arnold I. Miller, DO; Regional Oncol/Hematology Assoc, Kissimmee; and Harvey B. Sher, MD, Jacksonville Oncology Group, Jacksonville, FL; Jeremy K. Hon, MD, Huntsville Hospital, Huntsville; and Michael Meshad, MD, Providence Cancer Center, Mobile, AL; Robert O. Kerr, MD, Southwest Regional Cancer Center, Austin; Michael Ward, MD, Medical Arts Clinic, Lubbock; and Robyn Young, MD, Scott & White Clinic, Temple, TX; Leslie R. Laufman, MD, Columbus Community Clinical Oncology Program, Columbus; and Paula Silverman, MD, University Hospitals of Cleveland, Cleveland, OH; Deborah Lindquist, MD, Cancer Center at Sedona, Sedona; and Michael Roberts, MD, Hematology and Oncology Associates, Ltd, Phoenix, AZ; Alan P. Lyss, MD, Missouri Baptist Cancer Center, St. Louis; and Kelly B. Pendergrass, MD, Kansas City Internal Medicine, Kansas City, MO; Robert J. Meister, MD, Arlington-Fairfax Hematology-Oncology, PC, Arlington; and Nicholas J. Robert, MD, Fairfax-Prince William Hematology Oncology, Annandale, VA; Gerald P. Miletello, MD, Hematology Oncology Clinic, Baton Rouge, LA; David B. Myers, MD, BIOP, Billings, MT; Martin M. Oken, MD, Virginia Piper Cancer Institute, Minneapolis, MN; Frank Senecal, MD, HemOnc NW PC, Tacoma, WA; Peter T. Silberstein, MD, Mercy Cancer Center, North Iowa Mercy Health Center, Mason City, IA; Jack J. Sternberg, MD, Little Rock; and Bill L. Tranum, MD, Arkansas Oncology Clinic, Little Rock, AR; M. Roy Thomas, MD, Mid Dakota Clinic, Bismarck, ND; Stuart Tipping, MD, Marshfield Clinic, 3A Oncology, Marshfield, WI; and Charles R. Tweedy, MD, Amos Cancer Center, Columbus, GA.

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