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ORIGINAL REPORT

Phase III Study Comparing Exemestane With Tamoxifen As First-Line Hormonal Treatment of Metastatic Breast Cancer in Postmenopausal Women: The European Organisation for Research and Treatment of Cancer Breast Cancer Cooperative Group

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ABSTRACT

Purpose
This phase III randomized open-label clinical trial was designed to evaluate the efficacy and safety of the steroidal aromatase inactivator exemestane versus the antiestrogen tamoxifen as first-line treatment for metastatic breast cancer (MBC) in postmenopausal women.

Patients and Methods
The study was conducted at 81 centers and enrolled postmenopausal patients with measurable hormone-sensitive metastatic or locally advanced breast cancer. Prior adjuvant chemotherapy and/or tamoxifen were allowed. One previous chemotherapy regimen and no prior hormone therapy for advanced disease were permitted. Patients were randomly assigned to receive exemestane 25 mg or tamoxifen 20 mg orally once daily until disease progression or unacceptable toxicity occurred.

Results
A total of 371 patients enrolled at 79 sites (182 exemestane, 189 tamoxifen) were included in the analysis. Both treatments were generally well tolerated without major toxicity. Overall response rate was greater for exemestane than for tamoxifen treatment (46% *v* 31%; odds ratio = 1.85; 95% CI, 1.21 to 2.82; $P = .005$). Median progression-free survival (PFS) was longer with exemestane (9.9 months; 95% CI, 8.7 to 11.8 months) than with tamoxifen (5.8 months; 95% CI, 5.3 to 8.1 months). However, these early differences (Wilcoxon $P = .028$) did not translate to a longer-term benefit in PFS, the primary study end point (log-rank $P = .121$). There was also no difference in survival between both study arms.

Conclusion
Exemestane is an effective and well-tolerated first-line hormonal treatment for postmenopausal women with MBC and offers significant early improvement in time to tumor progression when compared with tamoxifen.

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INTRODUCTION

Tamoxifen, a competitive estrogen-receptor (ER) antagonist, was until recently the standard first-line hormonal therapy for metastatic hormone-receptor–positive breast cancer (MBC) in postmenopausal women.[1] The development of resistance to tamoxifen, and long-term toxicities including thromboembolic events and endometrial cancer, has led to increasing use of alternative hormonal therapies including exemestane (Aromasin; Pfizer Inc, New York, NY), a steroidal aromatase inactivator, and other aromatase inhibitors (AIs).

AIs inhibit the conversion of androgens into estrogens, thereby significantly reducing circulating estrogens in postmenopausal women. Their efficacy in breast cancer is well established.[2] Currently available AIs include the steroidal compound exemestane as well as nonsteroidal compounds such as anastrozole and letrozole.[3-5] Exemestane has been extensively investigated across the spectrum of hormone-receptor-positive postmenopausal breast cancer. Phase II studies have demonstrated its effectiveness as third-line therapy for breast cancer progressing after tamoxifen and nonsteroidal AIs.[4,6,7] Exemestane was also superior to megestrol acetate in

prolonging time to progression and even overall survival in patients who had progressed with tamoxifen.[8]

The European Organisation for the Research and Treatment of Cancer (EORTC) Breast Cancer Cooperative Group has investigated the efficacy and tolerability of exemestane compared with tamoxifen in first-line for hormone-responsive MBC in postmenopausal women. The phase II portion of the trial was designed to assess efficacy and safety of exemestane, with the intent to extend the trial into a randomized phase III in the event of promising results.[9] Additional safety studies focusing on lipids and endometrium were conducted in parallel.[10,11] Of 62 patients who received exemestane, 41% (95% CI, 29% to 53%) achieved an objective complete or partial response, whereas the remission rate for 60 tamoxifen-treated patients was 17% (95% CI, 7% to 27%).[9] A low incidence of clinically relevant toxicity was observed, and the criteria for extension into a phase III randomized trial were met.

The phase III study reported herein was specifically designed to compare the efficacy and safety of first-line therapy with exemestane versus tamoxifen in postmenopausal women with hormone-sensitive MBC, focusing on progression-free survival (PFS) as the primary study end point.

PATIENTS AND METHODS

Study Design

This was a multicenter, randomized open-label phase II/III study conducted at 81 centers. All phase II data were incorporated into this report. Eligible patients were randomly assigned to receive either exemestane (25 mg) or tamoxifen (20 mg) orally once daily. Central randomization was performed at the EORTC Data Center in a 1:1 ratio, using the minimization method[12] based on stratification for institution, previous adjuvant tamoxifen (yes *v* no), previous chemotherapy for metastatic disease (yes *v* no), and dominant metastatic site (visceral ± others *v* bone only *v* bone and soft tissue *v* soft tissue only). Patients received the designated treatment until disease progression or occurrence of unacceptable toxicity. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by all local ethics boards.

Patients

Eligibility criteria were similar to those of the phase II part of the trial.[9] Patients had to provide written informed consent before study participation. Female patients with metastatic or locally recurrent inoperable breast cancer with at least one bidimensionally measurable lesion were eligible, provided that they were postmenopausal, either by natural installation or after surgical castration. Patients with radiotherapy- or chemotherapy-induced amenorrhea lasting at least 1 year also were eligible, but for them and for any patient younger than age 56 years, follicle-stimulating hormone, luteinizing hormone, and plasma estradiol had to be within the postmenopausal range. Target lesions had to be measurable in two perpendicular diameters, with at least one diameter of at least 2.5 cm and not preirradiated. Exceptions included liver and extra-abdominal lesions that were followed by computed axial tomography (CT) of at least 2.0 cm; lesions followed by chest x-ray of at least 1.5 cm; photographed skin lesions of at least 1 cm; and purely lytic bone lesions identified by x-ray or CT scan, surrounded by calcified bone, at least 1 cm in diameter, and not previously irradiated unless they had clearly progressed since and the irradiation had occurred at least 3 months before. Primary tumors or metastases had to be hormone-receptor positive. Patients with hormone-receptor–unknown tumors were also eligible, provided that they had a disease-free interval (DFI) of at least 2 years since completing adjuvant therapy (or after surgery without adjuvant therapy). Prior adjuvant chemotherapy and/or tamoxifen were allowed, but the recurrence-free interval after tamoxifen had to be at least 6 months. No previous hormone therapy for MBC was allowed; previous radiotherapy and at most one previous chemotherapy regimen for metastatic disease were permitted, provided that the patient had recovered completely from treatment-associated acute toxicities. Patients with rapidly progressive disease, large-volume visceral disease, or brain metastases were excluded.

Treatment Protocol and Evaluations

Patients were instructed to take either exemestane or tamoxifen orally once daily after breakfast until disease progression or unacceptable toxicity. Patients were evaluated at baseline; at weeks 8, 16, and 24; then every 12 weeks until week 96; and thereafter every 24 weeks. Baseline assessments included a detailed history of previous treatments. A complete physical examination and laboratory evaluations were performed at baseline and at each follow-up visit.

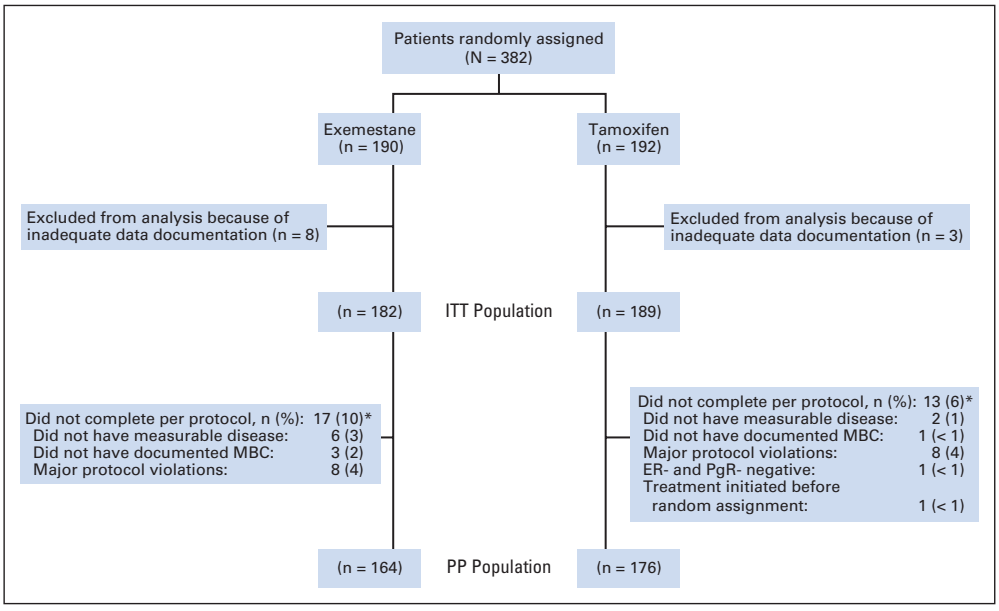

Fig 1. Patient flow. ER, estrogen receptor; PgR, progesterone receptor; ITT, intention to treat; MBC, metastatic breast cancer; PP, per protocol. (*) Patients may have had more than 1 reason for discontinuation.

Adverse events (AEs) were graded according to National Cancer Institute of Canada Common Toxicity Criteria (NCIC-CTC; December 1994 version) definitions. Tumor assessments at baseline comprised chest radiographs, bone scintigraphy, and imaging of target lesions. Tumor evaluations were made at 8-week intervals, using the same methods as at baseline. If the number of measurable lesions was too great, then up to eight representative lesions were selected. Tumor responses were classified using WHO criteria.[13] During the phase II part of the study, an independent panel of radiologists reviewed all objective responses. During the phase III trial, which focused on PFS, all case report forms were reviewed at the EORTC Data Center and by the study coordinator (R.J.P.) or the EORTC director (P.T.).

Study End Points

The primary efficacy end point for the phase III trial was PFS, defined as the length of time between random assignment and the onset of disease progression or death. When progressive disease (PD) was established, the time to progression was the time from random assignment until the day on which progression was suspected and documented. Progressive disease was defined as an increase of at least 25% in the size of at least one bidimensionally or unidimensionally measurable lesion or as the appearance of any new lesion. Appearance of pleural effusion or ascites with positive cytology were also considered to be PD. Pathologic fractures or bone collapse were not necessarily indicative of PD. The development of brain metastases was considered as PD even if disease elsewhere responded.

Secondary end points were overall survival (number of deaths at final analysis) and safety. The major safety end point was the incidence and severity of AEs based on NCIC-CTC grades.

Statistical Considerations

A hazard ratio (HR) of 0.71 in favor of exemestane was hypothesized based on earlier phase III trial data and the assumption that the median PFS would be 7.14 months with tamoxifen and 10.0 months with exemestane.[14-16] The study was designed to detect a 0.71 HR for PFS with 80% power by a two-sided log-rank test ($\alpha = 5\%$). To obtain this power, 278 events were required; therefore, based on the anticipated median PFS, 342 patients were to be enrolled. Data from the phase II and phase III portions of the trial were pooled for analysis.

All statistical analyses were based on the intention-to-treat (ITT) population. The Kaplan-Meier method was used to calculate PFS from the random assignment date until documented PD or death. Statistical testing was performed by log-rank test; associated HR values smaller than 1 are in favor of exemestane. Similar statistical methods were used for overall survival. An additional comparison of PFS was performed post hoc using the Wilcoxon test. Response rates were compared by χ^2 test and associated odds ratios.

Table 1. Baseline Characteristics

Characteristic	Treatment: Exemestane (n = 182) No.	%	Tamoxifen (n = 189) No.	%	All Patients (N = 371) No.	%
Age, years						
Median	63		62		63	
Range	37-86		37-87		37-87	
Disease-free interval, months						
Median	46		47		46	
Range	0-378		0-491		0-491	
WHO performance status						
0	84	46.2	80	42.3	164	44.2
1	79	43.4	84	44.4	163	43.9
2	19	10.4	25	13.2	44	11.9
Dominant metastatic site						
Visceral	87	47.8	88	46.6	175	47.2
Bone only	21	11.5	22	11.6	43	11.6
Bone + soft tissue	43	23.6	45	23.8	88	23.7
Soft tissue	31	17.0	34	18.0	65	17.5
ER/PgR status						
ER+/PgR+	104	57.1	106	56.1	210	56.6
ER+/PgR−	42	23.1	52	27.5	94	25.3
ER+/PgR unknown	14	7.7	11	5.8	25	6.7
ER–/PgR+	8	4.4	9	4.8	17	4.6
ER–/PgR−	0	0.0	1	0.5	1	0.3
Both unknown	14	7.7	10	5.3	24	6.5
Prior treatments						
Prior radiotherapy	75	41.2	79	41.8	154	41.5
Previous systemic therapy	76	41.7	79	41.8	154	41.5
Chemotherapy only	38	20.9	38	20.1	76	20.5
Hormone therapy only	21	11.5	16	8.5	36	9.7
Both chemotherapy and hormone therapy	17	9.3	25	13.2	42	11.3
Previous chemotherapy	55	30.2	63	33.3	118	31.8
Adjuvant treatment only	44	24.2	51	27.0	95	25.6
Metastatic disease only	8	4.4	8	4.2	16	4.3
Both adjuvant and metastatic	3	1.6	4	2.1	7	1.9
Previous adjuvant tamoxifen	38	20.9	39	20.6	77	20.8

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

Values greater than 1 reflect better odds for response to exemestane. A Cox proportional hazards model was used as an exploratory analysis, with backward and forward selection, while stratifying for treatment, to select a prognostic model.

The 5% level was used as cutoff for statistical significance throughout the study including exploratory analyses. Patients who did not experience an event (progression and/or death) by the time of analysis were censored at the last available follow-up date. Analyses of AEs were descriptive and were summarized as the worst grade of toxicity per patient.

RESULTS

Patients

Between October 1996 and December 2002, 382 patients were randomly assigned to receive exemestane (n = 190) or tamoxifen (n = 192). Two sites, which enrolled 11 patients, were excluded from analysis because of inadequate documentation, leaving 79 sites with 371 assessable patients (182 exemestane, 189 tamoxifen), who were analyzed on an ITT basis. The flow of participants through the study is summarized in Figure 1.

Baseline characteristics of the ITT population are depicted in Table 1. Demographics were similar in both treatment groups. Most of the tumors (93%) were ER and/or progesterone-receptor positive. Most patients (73%) had two or more involved metastatic sites. In each treatment arm, an identical proportion of patients (58%) had not previously received any systemic treatment.

Patient data were collected through May 12, 2004, with a median follow-up of 29 months (interquartile range, 20 to 53 months). The median treatment duration was 6.57 months for tamoxifen (95% CI, 5.78 to 10.91 months) and 11.50 months for exemestane (95% CI, 10.18 to 13.54 months). In the exemestane- and tamoxifen-treated groups, 159 (87.4%) and 168 (88.9%) patients discontinued treatment, respectively. The principal reason for discontinuation was PD in 136 patients (74.7%) receiving exemestane and 138 (73%) receiving tamoxifen. The remaining patients who discontinued did so for reasons other than PD, but only one patient with exemestane and two patients with tamoxifen stopped treatment because of toxicity. Forty-four patients remain without confirmation of treatment discontinuation, and their data were censored at their last known treatment date.

Efficacy Analyses

PFS. A total of 319 events (progression or death) were observed: 161 (85%) in the tamoxifen arm and 158 (87%) in the exemestane arm. The associated HR was 0.84 (95% CI, 0.67 to 1.05) in favor of exemestane. The HR for the 79% of patients without prior hormonal treatment was 0.83 in favor of exemestane. In addition, at both 6 and 12 months, the percentage of patients without disease progression was greater with exemestane (66.2% [95% CI, 59.3% to 73.1%] and 41.7% [95% CI, 34.5% to 48.9%], respectively) than with tamoxifen (49.5% [95% CI, 42.2% to 56.6%] and 31.2% [95% CI, 24.4% to 37.9%]). Although results of the log-rank test analysis were not statistically significant ($P = .121$), observation of the Kaplan-Meier curves (Fig 2A) indicated that the HR was not constant over time, with apparently greater differences in the earlier part of the follow-up period. Indeed, the 4.1-month difference in median PFS between treatment arms (Table 2) was statistically significant using the Wilcoxon test

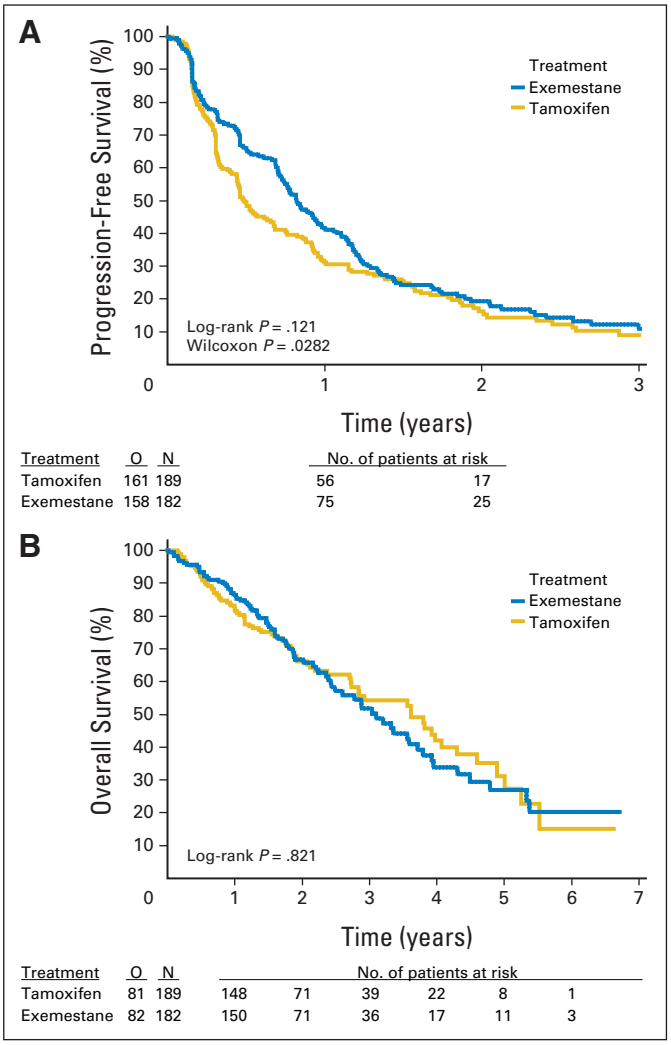

Fig 2. (A) Progression-free and (B) overall survival. O, total number of events observed; N, total number of patients.

($P = .028$), which gives greater weight to earlier events. In a follow-up analysis of key end points after a median of 46 months, the HR for PFS was similar at 0.87 (95% CI, 0.70 to 1.08).

We undertook exploratory analyses of PFS by potential prognostic factors. Regardless of treatment, patients with only one involved site ($P = .0001$) and those older than 65 years ($P = .014$) had a longer PFS. Dominant metastatic site, double-receptor phenotype, previous chemotherapy, previous hormonal therapy, DFI, performance status, and body mass index did not have prognostic value.

Finally, the results of sensitivity analyses including the 11 patients excluded because of inadequate documentation did not differ from those reported for the 371 assessable patients (data not shown).

Overall survival. As shown in Table 2 and illustrated in Figure 2B, no differences in overall survival were observed between treatment arms (log-rank $P = .821$). The 1-year survival rates in the tamoxifen and the exemestane groups were 82% and 86%, respectively. The HR for overall survival was 1.04 (95% CI, 0.76 to 1.41) after 29 months follow-up. At the 49-month updated analysis, 163 patients had died, 81 in the tamoxifen arm and 82 in the exemestane arm, and the HR remained essentially the same (HR = 1.13; 95% CI, 0.85 to 1.50).

Table 2. Efficacy Results

Result	Exemestane (n = 182) No.	Exemestane (n = 182) %	Tamoxifen (n = 189) No.	Tamoxifen (n = 189) %
PFS events	158	87	161	85
Median PFS, months	9.9		5.8	
95% CI	8.7 to 11.8		5.3 to 8.1	
PFS at 6 months	66.2		49.4	
95% CI	59.3 to 73.1		42.2 to 56.6	
PFS at 12 months	41.7		31.2	
95% CI	34.5 to 48.9		24.24 to 37.9	
OS events	82	45	81	43
Median OS, months	37.2		43.3	
95% CI	29.2 to 45.5		32.8 to 51.6	
OS at 12 months	86.4		82.0	
95% CI	81.3 to 91.5		76.4 to 87.6	
Complete response	15	8.2	6	3.2
Partial response	68	37.4	53	28.0
No change	54	29.7	67	35.4
Progressive disease	33	18.1	54	28.6
Early death/malignant disease	0	0.0	1	0.5
Early death/other	3	1.6	1	0.5
Not assessable	9	4.9	7	3.7

Abbreviation: OS, overall survival; PFS, progression-free survival.

Tumor Response and Prognostic Factors

As shown in Table 2, the objective response rate (complete response + partial response) was 46% for exemestane and 31% for tamoxifen. Consistent with the higher response rate in favor of exemestane (odds ratio = 1.85; 95% CI, 1.21 to 2.82; exact χ^2 $P = .005$), there were fewer patients with disease progression at 29-month follow-up with exemestane (33 patients [18.1%]) than with tamoxifen (54 patients [28.6%]).

Response rates by prognostic factors and treatment arm are shown in Table 3. With the exception of patients who received previous adjuvant tamoxifen, in whom response rates were nearly identical for both study arms, response rates for exemestane-treated patients were higher than for tamoxifen-treated patients in each prognostic subgroup.

Safety

Both treatments were generally well tolerated, and no treatment-related deaths were reported. The incidence of AEs is shown in Table 4 as the worst grade recorded per patient. In total, 61 grade 3/4 nonhematologic AEs were observed with tamoxifen versus 41 with exemestane, and 21 grade 3/4 events related to laboratory testing (hematology or chemistry) were recorded with tamoxifen versus 30 with exemestane. Serious AEs were infrequent, and a causal relationship with

Table 3. Response Rates by Prognostic Factors

Prognostic Factor	Exemestane (n = 182) No. of Responses	Exemestane (n = 182) No. of Patients	Exemestane (n = 182) %	Tamoxifen (n = 189) No. of Responses	Tamoxifen (n = 189) No. of Patients	Tamoxifen (n = 189) %
Dominant site						
Visceral	38	87	44	27	88	31
Bone only	10	21	48	3	22	14
Bone and soft tissue	18	43	42	16	45	36
Soft tissue only	17	31	55	13	34	38
Receptor status						
ER+ and PgR+	51	104	49	43	106	41
ER+ or PgR+	22	50	44	13	61	21
Previous therapy						
None	52	106	49	35	110	32
Hormonal (adjuvant tamoxifen)	7	21	33	6	16	38
Chemotherapy	17	38	45	14	38	37
Hormonal and chemotherapy	7	17	41	4	25	16

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

Table 4. Adverse Event Profile by Treatment (grades 1 to 4)

Adverse Event	% Exemestane (n = 182) Grade 1/2	Exemestane (n = 182) Grade 3/4	Tamoxifen (n = 189) Grade 1/2	Tamoxifen (n = 189) Grade 3/4
Nonhematologic events				
Alopecia	3.8	0	1.1	0
Anorexia	10.4	0.5	9.5	1.1
Anxiety	11.0	0	7.4	0
Arthralgias	11.5	0	5.3	0
Cardiac dysrhythmia	5.4	1.6	1.6	1.1
Cardiac dysfunction	4.4	0.5	3.2	0.5
Constipation	8.2	0	12.2	0
Cough	14.8	0	15.9	0
Deep venous thrombosis	1.6	0	1.6	0.5
Depression	7.7	0.5	6.9	0.5
Diarrhea	8.8	0	2.6	0
Dyspnea	13.7	1.6	13.2	2.6
Edema	9.9	1.1	10.1	1.1
Fatigue/malaise/lethargy	35.7	1.1	35.4	1.1
Gastrointestinal	8.2	0	11.6	0.5
Genitourinary	4.9	0	5.3	0
Hot flashes	34.6	0.5	38.1	0
Hypertension	8.2	3.3	2.6	3.2
Infection	15.4	1.1	12.2	0
Insomnia	9.9	0	5.3	0
Musculoskeletal	4.9	0.5	0.5	1.1
Nausea	17.0	0	19.0	0.5
Neurologic, dizziness	11.5	0	10.1	0
Neurologic, sensory	8.8	0.5	9.5	1.1
Pain, bone	29.1	3.8	29.1	5.8
Pain, other	31.9	2.7	27.5	3.2
Phlebitis	0	0	0.5	0.5
Skin	11.0	0.5	9.5	0
Sweating	10.4	0	9.0	0
Vaginal bleeding	1.1	0	3.2	0.5
Vaginal discharge	2.2	0	6.9	0
Vomiting	8.2	0	6.9	0
Weight loss	16.5	0.5	14.8	1.1
Weight gain	17.6	1.1	12.2	0.5
Hematologic events*				
Leukopenia	17.6	0	18.0	0
Neutropenia	9.9	1.1	13.8	0
Thrombocytopenia	4.4	1.6	11.6	0.5
Anemia	28.0	1.1	34.9	1.1
Biochemical changes*				
Creatinine	7.1	1.6	4.2	0
Bilirubin	11.5	3.3	1.1	1.6
AST	49.5	4.9	50.8	4.8
ALT	56.6	7.7	46.0	4.2

*Values missing for less than 10% of patients.

treatment was rarely established. Patients in both arms of the study experienced symptoms related to estrogen suppression; however, most of these were mild to moderate in severity. Patients treated with exemestane had fewer complaints of grade 2/3 hot flashes (6.5% *v* 12.2%) but more grade 1/2 arthralgia/myalgia, more cardiac dysrhythmia and cardiac dysfunction, and more grade 1 diarrhea. Tamoxifen-treated patients reported vaginal discharge or mild bleeding more frequently, and also more grade 2 edema. There was no obvious trend for weight change in either group. The incidence of phlebitis and deep vein thrombosis was low: one patient with exemestane had pulmonary embolism that was deemed to be disease related.

DISCUSSION

This phase III study compared exemestane and tamoxifen as first-line therapy for postmenopausal women with MBC. The median PFS with exemestane was 9.9 months (95% CI, 8.7 to 11.8 months) compared with 5.8 months (95% CI, 5.3 to 8.1 months) with tamoxifen. The log-rank test did not show a statistically significant difference between the two PFS curves, and the Kaplan-Meier analysis (Fig 2A) indicated that the HR was not constant over time. The Wilcoxon test, more sensitive to earlier events and thus more clinically meaningful in a population of MBC patients with relatively short anticipated survival times, showed that the 4.1-month difference in PFS between treatment arms was significant ($P = .028$). This finding is in agreement with the significantly higher response rate observed with exemestane than with tamoxifen (46% *v* 31%). Response rates by potential prognostic factors remained consistently higher in the exemestane arm but did not differ significantly by prognostic factor. No differences between the arms were detected in overall survival. Although both treatments were well tolerated, patients receiving exemestane reported more grade 1/2 arthralgia/myalgia and cardiac-related AEs, whereas those receiving tamoxifen reported more vaginal discharge, mild bleeding, and grade 2 edema.

It is noteworthy that the improvement in medians was met as hypothesized. Corresponding to these medians, most patients had an event (progression or death) within the first year. Interpretation of the Kaplan-Meier curves should concentrate on the first 2 years after random assignment because by that time point almost all patients have either experienced progression or died.

Our results are consistent with those observed in other randomized phase III studies that compared AIs and tamoxifen as first-line therapy for MBC (Table 5).[14,15,17] In contrast to these previously reported trials, patients enrolled onto our study were required to have measurable disease. The difference in PFS found here in favor of exemestane is corroborated by a significantly better quality of response and did not emanate from any subgroup analysis. These findings in the metastatic setting support the growing body of evidence that AIs have broad utility throughout the spectrum of breast cancer and may have clinical advantages over tamoxifen. Exemestane demonstrated excellent tolerability and safety. Because it differs from nonsteroidal AIs such as anastrozole and letrozole in its irreversible inhibition of aromatase[4] and its efficacy in MBC patients whose disease progressed during treatment with nonsteroidal AIs,[7] this expands the options available for treating hormone-sensitive breast cancers.

The benefit of AIs has also been demonstrated in the adjuvant setting, as suggested by results of large randomized adjuvant clinical trials comparing anastrozole, letrozole, or exemestane with tamoxifen.[18-22] However, a recent meta-analysis of phase III clinical trials comparing AIs with tamoxifen in early breast cancer reported that cardiovascular AEs were more frequent with AIs, although the absolute difference was small (approximately 0.50%) and the number needed to harm was more than 180 patients.[23] Our data demonstrating more cardiac-related AEs for exemestane-treated patients is consistent with this finding. However, none of the cardiac events were life

Table 5. Randomized Phase III Studies of Aromatase Inhibitors Compared With Tamoxifen As Initial Therapy for Metastatic Breast Cancer

Study Characteristic	Anastrozole *v* Tamoxifen*	Anastrozole *v* Tamoxifen†	Letrozole *v* Tamoxifen‡	Exemestane *v* Tamoxifen§
Patients in study, No.	170 *v* 182	340 *v* 328	453 *v* 454	182 *v* 189
Overall response, %	21 *v* 17	33 *v* 33	32 *v* 21‖	46 *v* 31‖
TTP/PFS, months	11 *v* 6‖	8 *v* 8	9 *v* 6‖	10 *v* 6‖
ER unknown, %	11 *v* 11	56 *v* 54	34 *v* 33	14 *v* 11

Abbreviations: TTP, time to progression; PFS, progression-free survival; ER, estrogen receptor.
*Nabholtz, 2000.[14]
†Bonneterre, 2000.[15]
‡Mouridsen, 2003.[17]
§Present study.
‖Significant statistical difference in favor of the aromatase inhibitor ($P < .05$).

threatening in our trial, and a distinction cannot be accurately made between true AI-related cardiotoxicity and pure chance of occurrence. It has also been hypothesized that the higher AI-related cardiotoxicity in some adjuvant trials was actually a reflection of a cardioprotective effect of tamoxifen, which was not observed for patients receiving AIs.[21]

The expansion of hormonally based therapeutic options for all stages of hormone-sensitive breast cancer is encouraging. Ongoing research aimed at fully characterizing the efficacy, safety, and tolerability profile of exemestane and other AIs will help elucidate which agents are most appropriate at each stage of disease, as well as the optimal sequence in which they should be administered. The results of the present study in first-line treatment of MBC extend the positive survival findings previously obtained comparing exemestane to megestrol acetate in advanced disease after tamoxifen failure.[8] As in previous similar trials conducted with nonsteroidal AIs, however, there is no survival advantage to be expected by using first-line exemestane instead of tamoxifen in a palliative setting. For that reason, lengthening of PFS is worthwhile provided that it supports the preservation or improvement of quality of life. Quality of life is therefore an important end point to include in future comparable studies of AIs as first-line treatment of hormone-sensitive MBC.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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