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ORIGINAL REPORT

Exemestane Versus Anastrozole in Postmenopausal Women With Early Breast Cancer: NCIC CTG MA.27—A Randomized Controlled Phase III Trial

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ABSTRACT

Purpose
In patients with hormone-dependent postmenopausal breast cancer, standard adjuvant therapy involves 5 years of the nonsteroidal aromatase inhibitors anastrozole and letrozole. The steroidal inhibitor exemestane is partially non–cross-resistant with nonsteroidal aromatase inhibitors and is a mild androgen and could prove superior to anastrozole regarding efficacy and toxicity, specifically with less bone loss.

Patients and Methods
We designed an open-label, randomized, phase III trial of 5 years of exemestane versus anastrozole with a two-sided test of superiority to detect a 2.4% improvement with exemestane in 5-year event-free survival (EFS). Secondary objectives included assessment of overall survival, distant disease–free survival, incidence of contralateral new primary breast cancer, and safety.

Results
In the study, 7,576 women (median age, 64.1 years) were enrolled. At median follow-up of 4.1 years, 4-year EFS was 91% for exemestane and 91.2% for anastrozole (stratified hazard ratio, 1.02; 95% CI, 0.87 to 1.18; $P = .85$). Overall, distant disease–free survival and disease-specific survival were also similar. In all, 31.6% of patients discontinued treatment as a result of adverse effects, concomitant disease, or study refusal. Osteoporosis/osteopenia, hypertriglyceridemia, vaginal bleeding, and hypercholesterolemia were less frequent on exemestane, whereas mild liver function abnormalities and rare episodes of atrial fibrillation were less frequent on anastrozole. Vasomotor and musculoskeletal symptoms were similar between arms.

Conclusion
This first comparison of steroidal and nonsteroidal classes of aromatase inhibitors showed neither to be superior in terms of breast cancer outcomes as 5-year initial adjuvant therapy for postmenopausal breast cancer by two-way test. Less toxicity on bone is compatible with one hypothesis behind MA.27 but requires confirmation. Exemestane should be considered another option as up-front adjuvant therapy for postmenopausal hormone receptor–positive breast cancer.

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INTRODUCTION

Five years of anastrozole or letrozole, the nonsteroidal oral aromatase inhibitors, is superior to 5 years of tamoxifen and the most commonly prescribed adjuvant endocrine therapy for hormone-dependent early breast cancer in postmenopausal women.[1-3] Exemestane, the sole steroidal aromatase inhibitor, is superior to 5 years of tamoxifen when given for 2 to 3 years after 2 to 3 years of prior tamoxifen.[4] Exemestane given for 5 years is similar in efficacy to tamoxifen given for 2 to 3 years followed by 2 to 3 years of exemestane.[5] However, there has been no comparison of exemestane with a nonsteroidal aromatase inhibitor.

In contrast to the competitive, reversible inhibition of aromatase by nonsteroidal agents, exemestane, an irreversible suicide inhibitor, may suppress

estrogens more than anastrozole and may yield superior efficacy.[6] As treatment of metastatic disease, exemestane and the nonsteroidal agents anastrozole and letrozole are clinically partially non–cross-resistant, and with disease progression, switching from one class to the other can yield clinical response.[7,8]

Furthermore, a major risk of adjuvant aromatase inhibitors is accelerated bone resorption from estrogen suppression.[9] Exemestane exerts mild androgenic effects as a result of its steroidal structure, reflected by suppression of serum sex hormone–binding globulin levels at therapeutic doses.[10] Preclinical models and volunteer studies suggest that exemestane may have less net impact on bone than the nonsteroidals.[11,12] Thus, we hypothesized that exemestane might have advantages over anastrozole for first-line adjuvant treatment of hormone-dependent early breast cancer in postmenopausal women.

PATIENTS AND METHODS

Study Design

The NCIC Clinical Trials Group (NCIC CTG) MA.27 trial is a phase III cooperative group study that is a multicenter, multinational, randomized, open-label trial. Enrollment began in June 2003 (ClinicalTrials.gov identifier: NCT00066573) after approval by health regulatory authorities and centers' institutional review boards. MA.27 (Fig 1) originally had a factorial design, with random assignment to exemestane versus anastrozole, with or without celecoxib (hypothesized to also be an anticancer agent), in postmenopausal women with receptor-positive primary breast cancer. Random assignment to celecoxib was discontinued as a result of reports of cardiac toxicity.[13] Women enrolled during celecoxib random assignment were included in the comparison of exemestane and anastrozole, stratified by whether they had been randomly assigned to celecoxib (yes *v* no; n = 1,622) and concomitant prophylactic aspirin use (≤ 81 mg per day; yes *v* no; n = 2,209). After positive results in 2005 of anti–human epidermal growth factor receptor 2 (HER2) therapy in early breast cancer, trastuzumab was permitted in women with locally determined HER2-positive disease, and the protocol was amended to include stratification by trastuzumab (yes *v* no; n = 1,915).[14] Other stratification factors throughout the trial included lymph node status (negative, positive, or unknown) and receipt of prior adjuvant chemotherapy (yes *v* no; n = 7,576). After providing informed consent, patients were randomly assigned using a dynamic minimization algorithm[15] to open-label exemestane 25 mg or anastrozole 1 mg daily after a morning meal.

Funding was provided by the Canadian Cancer Society, the US National Cancer Institute, and Pfizer. Data were collected, managed, and analyzed by the NCIC CTG. The trial committee made the decision to publish the results. Manuscript writing was undertaken entirely by the first author, coauthors, and staff at the NCIC CTG central office, who vouch for the fidelity of the study to the protocol and for accuracy and completeness of the data.

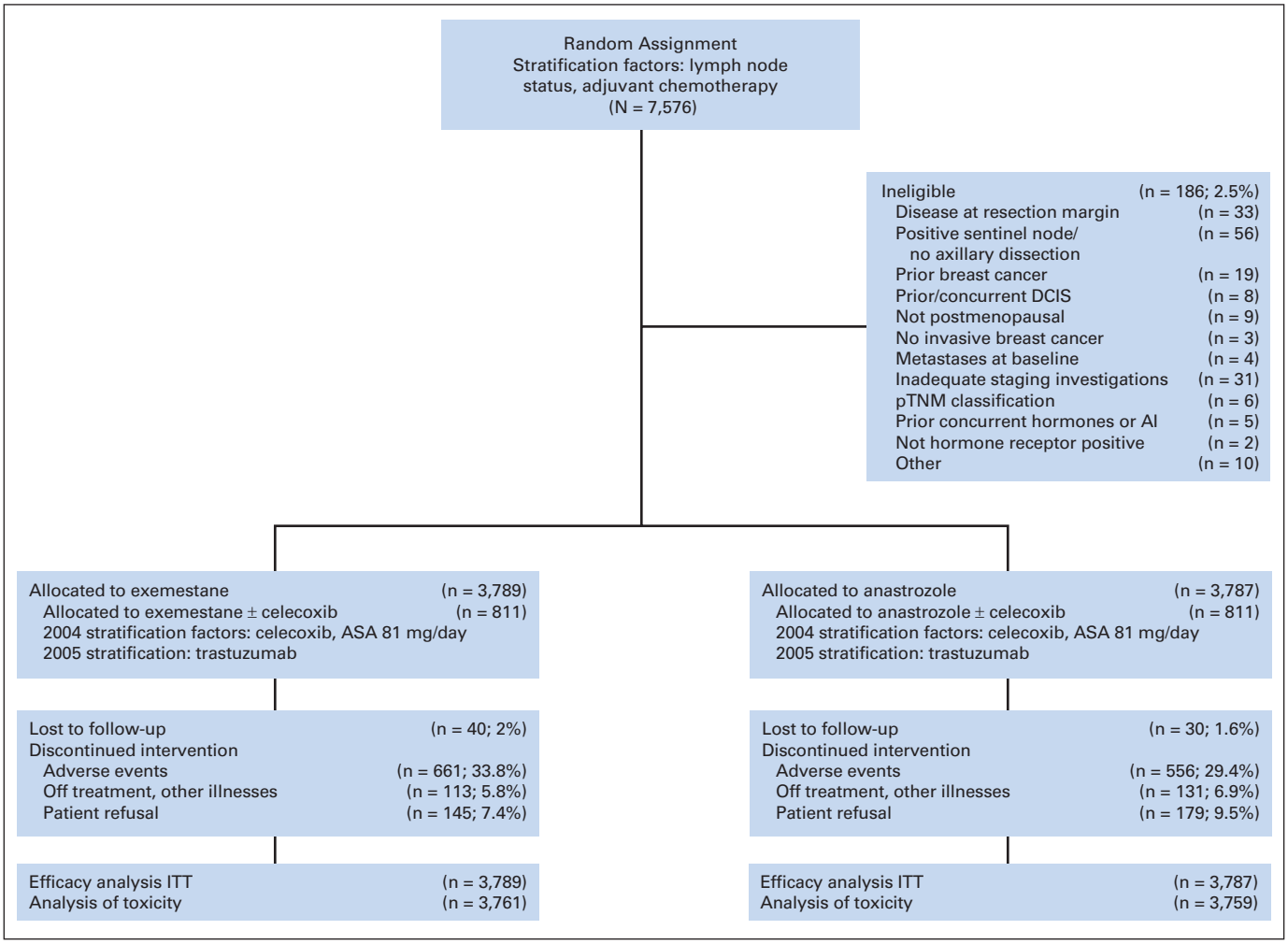

Fig 1. NCIC Cancer Clinical Trials Group MA.27 CONSORT diagram. AI, aromatase inhibitors; ASA, aspirin; DCIS, ductal carcinoma in situ; ITT, intent to treat.

Study Population

Eligibility criteria for MA.27 included the following: histologically confirmed, adequately excised, locally determined, hormone receptor–positive primary invasive breast cancer; postmenopausal status defined as age ≥ 60 years, age 45 to 59 years with either spontaneous cessation of menses for more than 12 months or spontaneous cessation of menses for less than 12 months and serum follicle-stimulating hormone level in the postmenopausal range before chemotherapy, or bilateral oophorectomy; random assignment more than 3 weeks and less than 3 months from completion of chemotherapy; an Eastern Cooperative Oncology Group performance status of 0, 1, or 2[16]; and minimum life expectancy of 5 years. Tumor grade was not available. Baseline imaging studies were performed to rule out metastatic disease in women who were symptomatic or had abnormal blood tests. Exclusion criteria included premenopausal status; hormone receptor–negative primary tumor; metachronous contralateral primary breast cancers (diagnosed at different times); history of other cancer, except nonmelanoma skin cancer or carcinoma in situ of the cervix; and prior tamoxifen. Raloxifene was allowed for bone health if stopped ≥ 3 weeks before random assignment.

Study End Points

The primary end point, event-free survival (EFS), was defined as time from random assignment to time of locoregional or distant disease recurrence, new primary breast cancer, or death from any cause. Secondary end points included overall survival, defined as time from random assignment to time of death from any cause; distant disease–free survival, defined as time from random assignment to time of distant disease recurrence; incidence of contralateral new primary breast cancer; and clinical and laboratory safety. Disease-specific survival, defined as time from random assignment to death with or from breast cancer, is also reported. Disease recurrence was defined pathologically or based on clinical or radiologic findings, and recurrences were dated at the time they were first detected. The trial was event driven, with a planned maximum duration of therapy in event-free patients of 5 years or until unacceptable toxicity developed.

Assessments

Baseline investigations included clinical evaluation, routine blood work, pathologic confirmation of primary tumor, mammogram within 12 months of random assignment, and chest x-ray and other imaging to rule out metastatic disease in symptomatic women or those with abnormal blood tests. On-study clinical evaluation, blood work, and evaluation of toxic effects were performed semi-annually during year 1 and annually thereafter; mammography was performed annually throughout the study. At baseline, women reported previous diagnoses of bone fractures, osteoporosis, or cardiovascular disease. Baseline symptoms and subsequent toxicities were graded according to Common Terminology Criteria for Adverse Events version 3.[17] Compliance was determined by pill count and self-reporting by patients at follow-up visits. New diagnoses were reported at follow-up visits. Treatment was discontinued for serious intercurrent illness, unacceptable toxic effects, or recurrence of disease or at the patient's request. Interim safety analyses were reviewed twice yearly by the Data and Safety Monitoring Committee. A subgroup of women in a companion quality-of-life study JMA27/E1Z03 completed the 56-item Functional Assessment of Cancer Therapy−Endocrine Symptoms. These results will be presented in a separate report.

Statistical Analysis

The MA.27 trial originally looked for an improvement in 5-year EFS from 78.2% on anastrozole to 81.8% on exemestane, with a planned accrual of 6,830 patients and a factorial design with or without celecoxib. Accrual was reduced to 5,800 patients when celecoxib was removed. In both instances, the trial had 90% power. The sample size was revised again when 68-month outcomes in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial[18] showed an estimated 5-year EFS rate on anastrozole of 86.5%. We also assumed that 15% of patients would receive trastuzumab, with a recurrence benefit of 1.0%, which yielded an expected 5-year EFS rate for those on the anastrozole arm of 87.5%. We maintained a hazard ratio (HR) of 0.80 between exemestane and anastrozole (ie, an improvement in 5-year EFS from 87.5% to 89.9%, similar to that obtained for anastrozole *v* tamoxifen in receptor-positive patients in the ATAC clinical trial[18]). With a two-sided 5% level test and 80% power, 6,840 patients and 630 events were needed for final analysis. An increase of 10% in the calculated sample size was permitted to adequately complete accrual to trial substudies. Two interim analyses were planned after 210 and 420 events. The α spending function of Lan and DeMets,[19] with O'Brien-Fleming boundaries, was used; the nominal significance level of the stratified log-rank test for EFS at the final analysis was $P = .0457$. The protocol was amended on March 9, 2009, to incorporate a test of futility at the second interim analysis,[20] which increased the events to 430 and 644 for the second interim and final analyses, respectively; the two-sided P values for significance were altered to $P = .0138$ and $P = .0448$, respectively.

Comparisons of time-to-event primary and secondary end points are based on the stratified log-rank test, adjusting for stratification factors at random assignment and applied by intent to treat to all randomly assigned patients. Survival was described by Kaplan-Meier plots. Exploratory stepwise forward Cox proportional hazards models were used to adjust the observed treatment effect for the influence of potential baseline prognostic factors and identify factors significantly associated with survival outcomes; a factor was added with Wald test statistic $P \leq .05$. Univariate and multivariate HRs and associated 95% CIs are reported. The cumulative incidences of new primary contralateral breast cancers are included. Fisher's exact test was used to compare adverse events between the exemestane and anastrozole groups.

RESULTS

Study Population

Between June 2, 2003, and July 31, 2008, 7,576 patients were randomly assigned, 3,789 to exemestane and 3,787 to anastrozole. After random assignment 186 women (2.5%) were deemed ineligible for a variety of reasons (Fig 1), including disease at the resection margin after lumpectomy (n = 33); no completion of axillary lymph node dissection after positive sentinel lymph nodes (n = 56); prior breast cancer (n = 19) or prior/concurrent contralateral ductal carcinoma in situ (n = 8); not postmenopausal (n = 9); no invasive breast cancer (n = 3); metastases at baseline (n = 4); inadequate staging investigations (n = 31); pTNM classification (n = 6); prior/concurrent hormones or aromatase inhibitors (n = 5); and not receptor positive (n = 2). Trial arms were balanced in terms of all relevant baseline characteristics (Table 1). The required number of events for the final analysis was reached in April 2010. All patients were included in the intent-to-treat analysis.

Study Outcome

At a median follow-up of 4.1 years, 693 EFS events occurred for final analysis. There were 350 events (9.2%) among women on exemestane versus 343 events (9.1%) on anastrozole. Figure 2 shows the Kaplan-Meier curves for EFS in the two groups. The estimated 4-year EFS rate was 91.0% for exemestane and 91.2% for anastrozole. The HR for EFS in the exemestane group compared with the anastrozole group was 1.02 (95% CI, 0.87 to 1.18; $P = .85$). Time to off-protocol treatment was not significantly different by arm (Fig 3; HR of exemestane compared with anastrozole, 1.06; 95% CI, 0.99 to 1.13; $P = .09$).

Summary results of the planned exploratory multivariate investigation of factor effects on EFS are listed in Table 2 (full results are listed in Appendix Table A1, online only). There were no significant treatment-factor interactions. The effect of exemestane and anastrozole on EFS was similar among 71% of women with node-negative disease (EFS, 93.2% at 4.0 years of median follow-up; stratified HR, 1.04; 95% CI, 0.85 to 1.27; $P = .73$) and 29% of women with node-positive disease (EFS, 85.8% at 4.0 years of median follow-up; HR,

Table 1. Baseline Patient Demographics and Clinical Characteristics

Characteristic	Exemestane (n = 3,789) No. of Patients	%	Anastrozole (n = 3,787) No. of Patients	%
Age, years				
< 60	1,233	33	1,221	33
< 70	1,466	39	1,497	40
≥ 70	1,090	29	1,069	28
Median	63.9		64.3	
Race				
White	3,593	95	3,558	94
Black	112	3	137	4
Other	84	2	92	3
ECOG performance status				
0	3,115	82	3,126	83
1	640	17	635	17
≥ 2	33	1	26	1
Missing	1	0	0	0
Primary surgery				
Partial mastectomy	2,609	69	2,554	67
Mastectomy	1,180	31	1,233	33
Tumor size				
T1	2,170	72	2,718	72
T2	977	26	959	25
T3-4/Tx/missing	102	2	110	3
Nodal status				
Negative	2,693	71	2,678	71
Positive/missing	1,096	29	1,109	29
Hormone receptor status				
ER positive	3,766	99	3,759	99
PR positive	3,085	81	3,005	79
Adjuvant chemotherapy				
Yes	1,163	31	1,164	31
No	2,626	69	2,623	69
Trastuzumab (since 2005)	957		958	
Yes	36	4	38	4
No	921	96	920	96
Concurrent bisphosphonate use				
Yes	409	11	400	11
No/unknown/not permitted	3,380	89	3,387	89
Prior raloxifene use				
Yes	64	2	52	1
No/unknown/missing	3,725	98	3,735	99

Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.

0.99; 95% CI, 0.79 to 1.23; $P = .90$). Likewise, EFS was similar between arms among the 69% of women who had not received adjuvant chemotherapy (HR, 1.01; 95% CI, 0.84 to 1.23; $P = .89$) and among the 31% of women who had (HR, 1.02; 95% CI, 0.80 to 1.29; $P = .89$).

In all instances, the significant factors for EFS were prognostic, with significantly worse EFS for women age 70 years or older (HR, 1.89; 95% CI, 1.35 to 2.66; $P < .001$) or with T2 tumors (HR, 1.69; 95% CI, 1.42 to 2.01; $P < .001$), T3-4/TX/missing tumors (HR, 1.62; 95% CI, 1.12 to 2.35; $P = .01$), N2-3 (HR, 2.33; 95% CI, 1.14 to 4.76; $P = .02$), left-sided tumors (HR, 1.96; 95% CI, 0.96 to 4.03; $P = .07$), or prior fractures (HR, 1.27; 95% CI, 1.01 to 1.59; $P = .04$). Patients with the following factors had significantly better EFS: bilateral oophorectomy, age 45 to 59 years, and less than 12 months after hysterectomy (HR, 0.46; 95% CI, 0.27 to 0.81; $P = .01$); Eastern Cooperative Oncology Group performance status of 0 (HR, 0.69; 95% CI, 0.58 to 0.82; $P < .001$); estrogen receptor–positive/progesterone receptor–positive tumors (HR, 0.79; 95% CI, 0.67 to 0.95; $P = .01$); prior radiotherapy (HR, 0.77; 95% CI, 0.65 to 0.91; $P = .002$); and adjuvant chemotherapy (HR, 0.31; 95% CI, 0.13 to 0.73; $P = .01$).

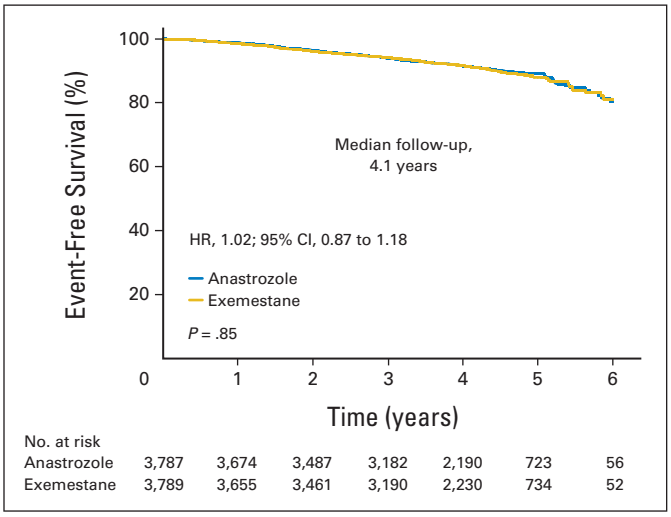

Fig 2. Kaplan-Meier estimates of event-free survival. HR, hazard ratio.

The frequency of events included in the primary end point among women receiving exemestane or anastrozole were distant metastases (138 *v* 138 patients, respectively), local in-breast recurrences (54 *v* 54 patients, respectively), death (114 *v* 122 patients, respectively), and contralateral new primary breast cancers (46 *v* 33 patients, respectively).

There was no significant difference in overall survival in the two treatment groups, with 208 deaths (5.5%) occurring on exemestane compared with 224 deaths (5.9%) on anastrozole (HR, 0.93; 95% CI, 0.77 to 1.13; $P = .46$). Deaths in the exemestane and anastrozole groups were from breast cancer (n = 187; 89 *v* 98 patients, respectively), cardiovascular causes (n = 66; 31 *v* 35 patients, respectively),

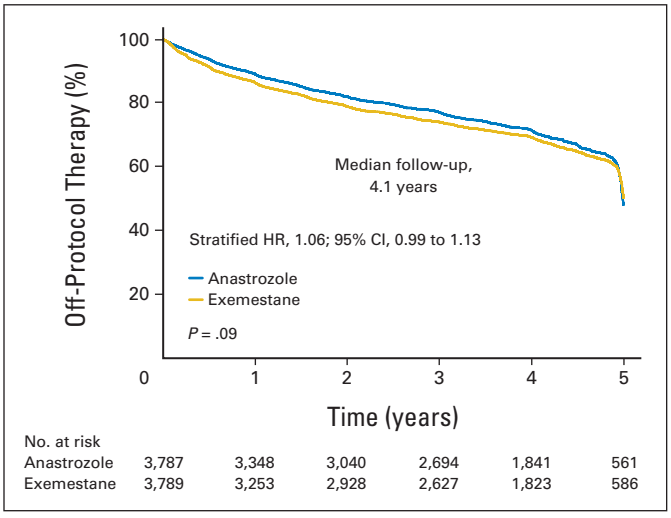

Fig 3. Time to off-protocol treatment for all patients. HR, hazard ratio.

Table 2. Summary of Treatment and Significant Multivariate Effects of Factors on Event-Free Survival

Factor*	Adjusted β†	SE	P	Hazard Ratio	95% CI
Treatment: exemestane *v* anastrozole	0.02	0.08	.76	1.02	0.88 to 1.19
Age, years					
≤ 59	Referent				
≥ 70	0.64	0.17	< .001	1.89	1.35 to 2.66
ECOG performance status					
Other than active	Referent				
0	−0.37	0.09	< .001	0.69	0.58 to 0.82
Hormone receptor status					
Other than ER positive/PR positive	Referent				
ER positive/PR positive	−0.23	0.09	.01	0.79	0.67 to 0.95
Tumor size					
T1	Referent				
T2	0.52	0.09	< .001	1.69	1.42 to 2.01
T3-4/Tx/missing	0.48	0.19	.01	1.62	1.12 to 2.35
Nodal status					
N0	Referent				
N2-3	0.85	0.36	.02	2.33	1.14 to 4.76
Prior fractures					
No prior fracture	Referent				
Prior fracture	0.24	0.12	.04	1.27	1.01 to 1.59
Prior adjuvant chemotherapy					
No prior chemotherapy	Referent				
Prior chemotherapy	−1.17	0.44	.01	0.31	0.13 to 0.73

NOTE. See Appendix Table A1 for full table.
Abbreviations: ECOG, Eastern Cooperative Oncology Group; ER, estrogen receptor; PR, progesterone receptor.
*Variables other than treatment were entered if Wald $P \leq .05$.
†Stratified multivariate stepwise Cox model for event-free survival with baseline characteristics: stratification factors from random assignment are nodal status, adjuvant chemotherapy, celecoxib use, aspirin use, and trastuzumab use. Treatment had forced inclusion throughout the stepwise model process.

Table 3. Adverse Events (all grades)

Adverse Event	Exemestane No. of Patients	Exemestane %	Anastrozole No. of Patients	Anastrozole %	P
Total	3,761	100	3,759	100	
Hot flashes	2,051	55	2,101	56	.24
Arthritis/arthralgia	253	7	231	6	.32
Muscle pain	649	17	606	16	.19
Vaginal bleeding	40	1	61	2	.04
ALT	53	1	23	1	.001
AST	47	1	19	1	.001
Bilirubin	59	2	24	1	< .001
Acne	12	0	3	0	.04
Masculinization	36	1	11	0	< .001
Myocardial infarction	38	1	32	1	.55
Stroke/transient ischemic attack	32	1	38	1	.47
Atrial fibrillation	72	2	46	1	.02
Hypertriglyceridemia	80	2	124	3	.002
Hypercholesterolemia	577	15	665	18	.01
Bisphosphonate use after random assignment	28	1	16	0	.10
Osteoporosis	1,171	31	1,304	35	.001
Any clinical fracture*	358	10	354	9	.91
Fragility fracture*	136	4	136	4	.98

NOTE. Seventy percent of adverse events were grade 1 or 2. Adverse events were graded according to Common Terminology Criteria for Adverse Events version 3.
*At anytime.

and other causes (n = 145; 68 *v* 77 patients, respectively). Race/ethnicity data were collected on this study. Exploratory investigation of race/ethnicity by treatment interaction was significant (HR, 0.38; 95% CI, 0.17 to 0.83; $P = .02$), with minority women on exemestane having fewer deaths than those on anastrozole. There were also significantly lower adverse event rates and lower discontinuation of study medication (24%) compared with white women (32%; Appendix Figs A1A and A1B, for eligible MA.27 patients with known race, and Appendix Table A2, online only). There was a significant T stage × treatment interaction ($P = .03$; HR, 0.78 for exemestane *v* anastrozole with T1 tumors; 95% CI, 0.60 to 1.01; HR, 1.17 with ≥ T2 tumors; 95% CI, 0.88 to 1.55). There was no significant difference between the exemestane and anastrozole groups in terms of distant disease–free survival (n = 157 [4.1%] *v* n = 164 [4.3%], respectively; HR, 0.95; 95% CI, 0.76 to 1.18; $P = .64$) or disease-specific survival (n = 89 [2.4%] *v* n = 98 [2.6%], respectively; HR, 0.93; 95% CI, 0.70 to 1.24; $P = .62$).

Safety

Compliance was poor, with a 31.6% discontinuation rate (33.8% and 29.4% in exemestane and anastrozole groups, respectively) for adverse effects, concomitant diseases, or study refusal (Appendix Table A2). Table 3 lists summary data on toxic effects and safety in the women enrolled onto the study, based on previously published profiles of drug effects by aromatase inhibitor–induced menopausal symptomatology, androgenicity of exemestane, effects on key end organs, and bone end points (Appendix Table A3, online only, lists toxicities with significant differences by treatment, and Appendix Tables A4 and A5, online only, list adverse events by race).

Menopause-like symptoms, including hot flashes, arthritis, arthralgia, and myalgia, were not significantly different between treatment groups. Abnormal postmenopausal vaginal bleeding was uncommon but seen more among women on anastrozole than exemestane (61 *v* 40 patients, respectively; $P = .04$). Mild liver function blood test abnormalities (bilirubin; 59 patients receiving exemestane *v* 24 patients receiving anastrozole) and symptoms of acne (12 patients on exemestane *v* three patients on anastrozole) and masculinization (36 patients on exemestane *v* 11 patients on anastrozole) were more frequent on exemestane. Myocardial infarction, stroke, and transient ischemic attacks were not significantly different between the groups. Atrial fibrillation was seen more frequently among women on exemestane than anastrozole (72 *v* 46 patients, respectively; $P = .02$). Hypertriglyceridemia (80 patients on exemestane *v* 124 patients on anastrozole; $P = .002$) and hypercholesterolemia (577 patients on exemestane *v* 665 patients on anastrozole; $P = .01$) were reported less frequently on exemestane. Self-reported new diagnoses of osteoporosis were significantly less frequent on exemestane than on anastrozole (1,171 patients [31%] *v* 1,304 patients [35%]; $P = .001$). The number of new clinical fractures on study medication was similar between groups ($P = .91$). Fractures at fragility sites occurred in 136 patients (4%) in each group ($P = .98$).

DISCUSSION

International guidelines[21-23] recommend 5 years of monotherapy with nonsteroidal aromatase inhibitors anastrozole and letrozole for first-line adjuvant therapy of hormone-dependent breast cancer in postmenopausal women. The addition of ovarian function suppression is being studied in premenopausal women in the Suppression of Ovarian Function Trial and the Tamoxifen and Exemestane Trial.[24] Tamoxifen monotherapy for 5 years remains an approved therapy; a switching strategy of tamoxifen for 2 to 3 years followed by 2 to 3 years of exemestane is associated with superior outcomes, whereas exemestane given for an initial up-front 5 years has not been shown to be superior to this switch.

Our study is the first, to our knowledge, to compare the two classes of aromatase inhibitors, steroidal versus nonsteroidal, as initial adjuvant therapy. We found that neither exemestane nor anastrozole was superior in terms of breast cancer outcomes (EFS, overall survival, distant disease–free survival, and disease-specific survival), although a protocol-specified investigation of factor effects raised the hypothesis that minority women on exemestane experienced less adverse symptomatology, less discontinuation, and fewer deaths. These findings would need confirmation in a larger patient population or a prospective trial before being of guidance in clinical practice.

Our study population reflects clinical practice in the United States, Canada, and Western Europe in terms of the following factors: median age of 64 years, predominantly white, approximately two thirds with lower risk node-negative disease, and the majority not having received adjuvant chemotherapy. Although there were efforts to recruit more women of races other than white, we were unsuccessful. The 4-year median EFS of 91% in both arms reflects the good prognosis of patients with estrogen receptor–positive breast cancer managed with current local and systemic adjuvant therapies. Compliance with chronic oral endocrine therapies is generally poor, with aromatase inhibitor treatment in particular associated with only 60% of women adherent by 3 years of an intended 5-year treatment.[25-27] Our compliance rates, although also not good, were similar for both trial arms and better than most adjuvant endocrine trials reported.[25-27] Only 25 patients of the total MA.27 trial population received more than 5 years of endocrine therapy, and therefore, we do not believe that cross-over to another therapy or more than 5 years of extended therapy could have affected our trial results.[28] No treatment-related deaths attributable to either aromatase inhibitor were noted in our study. It had been hoped that the mild androgenic effect of exemestane would lessen hot flashes and urogenital toxicity. We found no evidence of differences in menopausal-like symptoms provoked by the significant lowering of circulating estrogen levels by these two potent aromatase inhibitors, although some important safety and toxic adverse effects were different between the two inhibitors. New diagnoses of self-reported osteoporosis, including osteopenia by Common Terminology Criteria for Adverse Events, occurred less on exemestane, with similar bisphosphonate use at baseline and during the treatment period on the two arms. A specific substudy of bone mineral density changes in approximately 500 women randomly assigned in MA.27 has been conducted, and preliminary results indicating less bone mineral density loss on exemestane than anastrozole were presented at the 47th Annual Meeting of the American Society of Clinical Oncology in 2011.[29] Clinical bone fractures on study were similar between groups, as were serious adverse cardiovascular events. Although more patients developed mild abnormal lipid levels on anastrozole, rare episodes of atrial fibrillation were more common on exemestane. Exemestane also produced mild and clinically insignificant liver function test abnormalities, low-grade symptoms of acne, and masculinization, compatible with its mild androgenic action. We recognize the possibility that the open-label nature of the trial might have had an influence on the reporting of adverse events, but we were unable to obtain placebo pills for anastrozole.

In our findings, exemestane was not superior to anastrozole as postulated; in addition, anastrozole was not superior to exemestane by two-way test. These drugs had a somewhat different adverse effect profile, particularly concerning the effect of exemestane on bone health. The latter finding will be evaluated more fully in our bone substudy. Given these results, exemestane should now be considered another safe and effective option in addition to anastrozole or letrozole as initial adjuvant therapy for patients with hormone receptor–positive postmenopausal breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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