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A Randomized Trial of Exemestane after Two to Three Years of Tamoxifen Therapy in Postmenopausal Women with Primary Breast Cancer

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ABSTRACT

BACKGROUND

Tamoxifen, taken for five years, is the standard adjuvant treatment for postmenopausal women with primary, estrogen-receptor–positive breast cancer. Despite this treatment, however, some patients have a relapse.

METHODS

We conducted a double-blind, randomized trial to test whether, after two to three years of tamoxifen therapy, switching to exemestane was more effective than continuing tamoxifen therapy for the remainder of the five years of treatment. The primary end point was disease-free survival.

RESULTS

Of the 4742 patients enrolled, 2362 were randomly assigned to switch to exemestane, and 2380 to continue to receive tamoxifen. After a median follow-up of 30.6 months, 449 first events (local or metastatic recurrence, contralateral breast cancer, or death) were reported — 183 in the exemestane group and 266 in the tamoxifen group. The unadjusted hazard ratio in the exemestane group as compared with the tamoxifen group was 0.68 (95 percent confidence interval, 0.56 to 0.82; $P < 0.001$ by the log-rank test), representing a 32 percent reduction in risk and corresponding to an absolute benefit in terms of disease-free survival of 4.7 percent (95 percent confidence interval, 2.6 to 6.8) at three years after randomization. Overall survival was not significantly different in the two groups, with 93 deaths occurring in the exemestane group and 106 in the tamoxifen group. Severe toxic effects of exemestane were rare. Contralateral breast cancer occurred in 20 patients in the tamoxifen group and 9 in the exemestane group ($P = 0.04$).

CONCLUSIONS

Exemestane therapy after two to three years of tamoxifen therapy significantly improved disease-free survival as compared with the standard five years of tamoxifen treatment.

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BREAST CANCER IS ESTROGEN-DEPENDENT in many cases, and reducing the estrogen levels by means of ovariectomy can cause regression of established disease,¹ especially if the tumor is rich in estrogen receptors.² The selective estrogen-receptor modulator tamoxifen blocks the action of estrogen by binding to one of the activating regions of the estrogen receptor.^{3,4} When given to women with estrogen-receptor-positive breast cancer for five years after surgery, tamoxifen reduces the risk of recurrence by 47 percent and the risk of death by 26 percent.⁵ The risk-benefit ratio of using tamoxifen for longer than five years remains unclear,^{6,7} and trials addressing this question are ongoing. International guidelines recommend that patients should not receive adjuvant tamoxifen therapy for more than five years outside the context of a clinical trial.⁸

Alternative endocrine therapy is often effective after disease has relapsed despite tamoxifen treatment, since at that point, estrogen receptors are still present in most patients.⁹ Several trials have confirmed the superiority of aromatase inhibitors over progestins in this setting.^{10,11} Aromatase is an enzyme that catalyzes the conversion of androgens to estrogens. There are two classes of third-generation oral aromatase inhibitors: irreversible steroidal inactivators, exemplified by exemestane,^{12,13} and reversible nonsteroidal inhibitors, such as anastrozole and letrozole.¹⁴

Exemestane inhibits aromatization *in vivo* by about 98 percent.¹⁵ It is superior to megestrol acetate with respect to time to progression in advanced breast cancer¹⁴ and has antitumor effects in patients who have no response to third-generation nonsteroidal aromatase inhibitors.¹⁶ Preliminary results show that exemestane is superior to tamoxifen as first-line therapy for metastatic disease.¹⁷ Theoretically, exemestane should not cause endometrial thickening or endometrial cancer, which are occasionally observed after tamoxifen therapy.¹⁸

The Intergroup Exemestane Study (IES) was designed to investigate whether exemestane, when given to postmenopausal women who remained free of recurrence after receiving adjuvant tamoxifen therapy for two to three years for primary breast cancer, could prolong disease-free survival, as compared with continued tamoxifen therapy. Here we report the results of the second planned interim analysis, which we are releasing in accordance with the recommendation of the independent data and safety monitoring committee.

METHODS

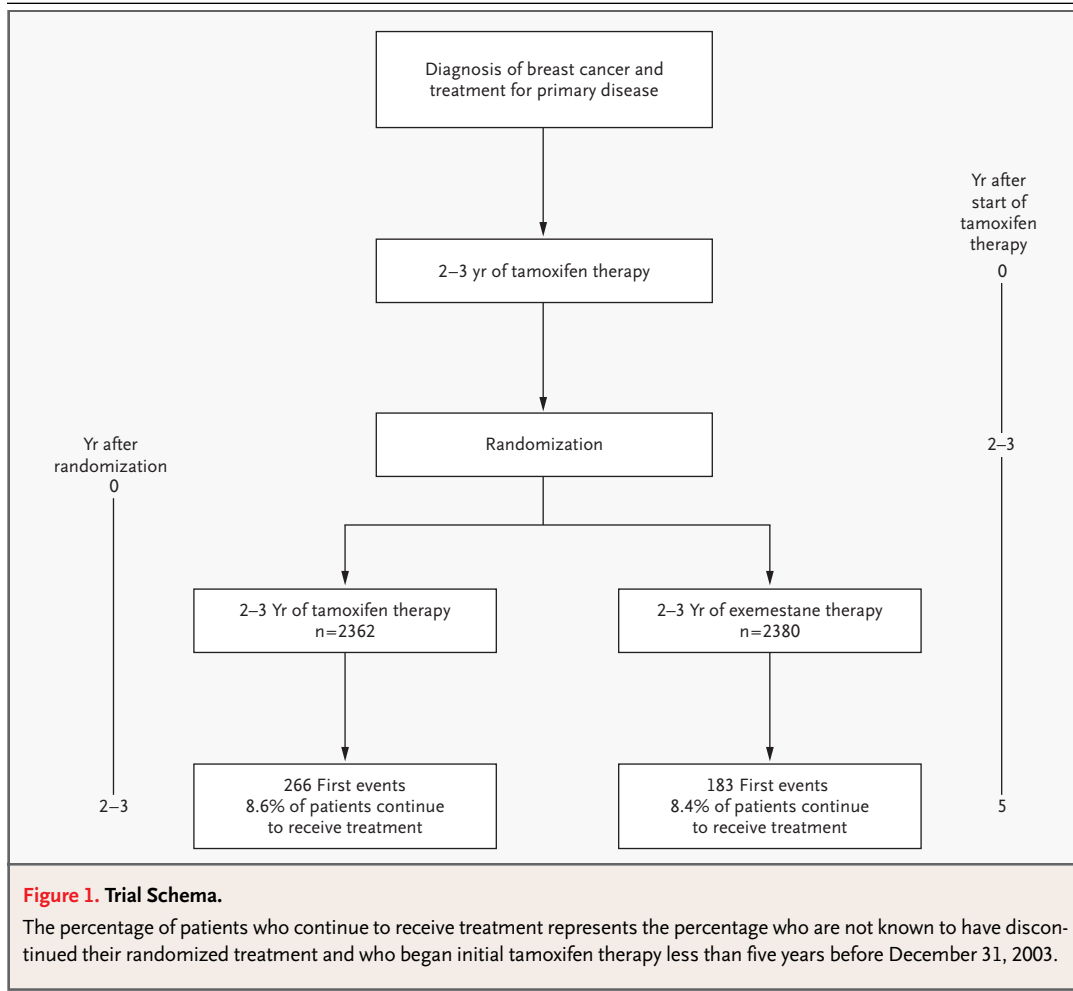
STUDY DESIGN

Our study is an international, intergroup, phase 3, randomized, double-blind trial comparing the efficacy and safety of continued adjuvant tamoxifen therapy with the efficacy and safety of exemestane therapy in postmenopausal women with primary breast cancer who remain free of disease after receiving adjuvant tamoxifen therapy for two to three years. Women were randomly assigned to receive oral exemestane (25 mg) or tamoxifen (20 mg) daily in order to complete a total of five years of adjuvant endocrine treatment (Fig. 1). Randomization was performed with the use of permuted blocks and was stratified according to center.

The primary end point was disease-free survival, defined by the time from randomization to recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause. Secondary end points included overall survival, the incidence of contralateral breast cancer, and long-term tolerability. For consistency and comparability with other reported trials,¹⁹ we also report breast-cancer-free survival, with censoring of deaths that occurred without a recurrence of breast cancer or a diagnosis of contralateral breast cancer. Results from substudies assessing the quality of life, uterine thickness, bone metabolism, and bone mineral density will be reported separately.

The study was coordinated by the International Collaborative Cancer Group (ICCG), Imperial College London, and conducted under the auspices of the Breast International Group (BIG). The trial was governed by a steering committee comprising representatives from the ICCG, participating cooperative groups, BIG, and the pharmaceutical-industry sponsor. Data for each cooperative group were collected by the group's data center and collated centrally by the ICCG Data Center. Central review and querying and analysis of data were undertaken by the ICCG Data Center in collaboration with the Institute of Cancer Research, where the independent statisticians were based. The sponsor had no access to the trial data base or interim analyses. The study was overseen by a data and safety monitoring committee that was independent of the ICCG Data Center, the steering committee, and the sponsor.

The institutional review board at each participating institution approved the study protocol, and all patients gave written informed consent. Randomization was performed by the data center for



each cooperative group or through the ICGG Data Center.

ELIGIBILITY CRITERIA

Patients were eligible if they had histologically confirmed, completely resected unilateral invasive breast carcinoma that was positive for estrogen receptors (as determined by means of standard immunostaining procedures) or that was of unknown receptor status. Patients were postmenopausal (55 years of age or older with amenorrhea for more than two years, or amenorrhea for more than one year at the time of diagnosis) and had received adjuvant tamoxifen therapy for at least two years but not more than three years and one month. Most patients (95 percent) received tamoxifen at a dose of 20 mg daily, but patients who received 30 mg daily were eligible (and continued to receive the same dose if they were assigned to the tamoxifen group).

Patients were required to have adequate hematologic, renal, and liver function at the time of randomization (defined as a normal blood count, a serum creatinine concentration less than 1.5 times the upper limit of normal, and a serum alanine aminotransferase concentration less than 2.5 times the upper limit of normal).

The criteria for exclusion included the presence of a tumor with known negative estrogen-receptor status; evidence of local relapse or a distant metastasis since the time of diagnosis; a clinically significant skeletal, cardiac, or endocrine disorder; and the use of hormone-replacement therapy within four weeks before randomization. Patients were also excluded if they had clinical evidence of severe osteoporosis or a history of a previous neoplasm other than carcinoma in situ of the cervix or basal-cell skin carcinoma or if they were taking concomitant anti-coagulant agents, a selective estrogen-receptor

modulator other than tamoxifen, or any other form of hormonal therapy.

The protocol required adequate treatment of primary disease, including postoperative radiotherapy in patients who had been treated with breast-preserving surgery. Neoadjuvant chemotherapy was permitted according to a consistent policy within each center. Patients were required to have started chemotherapy within three months after diagnosis and to have begun receiving tamoxifen and radiotherapy within three months after the completion of chemotherapy.

FOLLOW-UP PROCEDURES

Symptoms, side effects, findings on clinical examination, and the level of compliance with treatment were recorded at three-month intervals during the first year after randomization, every six months during the second and third years, and annually thereafter. Hematologic and biochemical analyses and mammography (if the local procedure permitted) were performed annually.

STATISTICAL ANALYSIS

Enrollment of 4400 patients was required in order to detect an absolute difference of 3.6 percent in disease-free survival three years after randomization (with 88 percent power and a two-sided level of significance of 4.3 percent after adjustment for interim analyses). The a priori expectation was that the principal analysis would be conducted after 716 end-point events had occurred. Three interim efficacy analyses were to be conducted, with the use of O'Brien–Fleming stopping boundaries, after one quarter, one half, and three quarters of the planned total number of events. Emerging trial data and interim analyses were reviewed by the independent data and safety monitoring committee, whose terms of reference dictated that their decisions be guided (but not mandated) by the above stopping rules.

Analyses were performed according to the intention-to-treat principle and included all patients who underwent randomization. All data were censored on June 30, 2003, but the snapshot of data used for the analysis of efficacy was updated to include all data received by the ICCG Data Center through December 31, 2003. Log-rank tests were used to compare the two groups. Two-sided P values and 95 percent confidence intervals are reported. Cox proportional-hazards regression was used to adjust for prespecified prognostic factors.²⁰ Hazard ratios of less than 1.0 favor exemestane. Kaplan–

Meier time-to-event curves are presented. The groups were compared in terms of the incidence of adverse effects with the use of chi-square tests. Because of the early release of the efficacy results, data on adverse events are provisional; the validation process is ongoing. Here, we emphasize the adverse effects for which there is a difference between groups with a P value of 0.01 or less.

RESULTS

STUDY POPULATION

We recruited 4742 women from 37 countries and 20 cooperative groups between February 1998 and February 2003. Recruitment continued beyond the target enrollment of 4400 in order to complete accrual to the substudies on the effects on bone and quality of life. The median follow-up was 30.6 months (interquartile range, 23.9 to 36.6). The two groups were balanced with regard to base-line characteristics (Table 1). A total of 192 patients were subsequently found to be ineligible (16 because of previous breast cancers, 31 because of previous other cancers, 74 because they had undergone breast-conserving surgery but had not received radiotherapy, 25 because they were of uncertain menopausal status, 24 because they had known estrogen-receptor–negative tumors, 8 because they had used hormone-replacement therapy within four weeks before randomization, and 14 for other reasons); these patients are included in all analyses on an intention-to-treat basis.

EFFICACY

The second interim analysis, which was triggered by the reporting of 358 events, was presented to the data and safety monitoring committee on December 2, 2003, and included all data that had been received relating to events and follow-up through June 30, 2003. At that meeting, the committee recommended that key efficacy data be released, because the O'Brien–Fleming stopping boundary ($P=0.004$) had been exceeded. The steering committee agreed to the release at a meeting on December 3, 2003. This report constitutes a refined analysis of that presented to the data and safety monitoring committee.

A total of 449 first events were reported: 183 in the exemestane group and 266 in the tamoxifen group (Table 2). The unadjusted hazard ratio in the exemestane group as compared with the tamoxifen group was 0.68 (95 percent confidence interval, 0.56

Table 1. Base-Line Characteristics of the Patients and Tumors and Primary Treatment.*

Variable	Exemestane (N=2362)	Tamoxifen (N=2380)
Demographic characteristics		
Age — yr	64.3±8.1	64.2±8.2
White race — no. (%)	2308 (97.7)	2325 (97.7)
Nodal status — no. (%)		
Negative	1211 (51.3)	1211 (50.9)
1–3 Positive nodes	715 (30.3)	706 (29.7)
≥4 Positive nodes	321 (13.6)	330 (13.9)
Positive, but no. of nodes missing	5 (0.2)	9 (0.4)
Unknown	84 (3.6)	96 (4.0)
Missing data	26 (1.1)	28 (1.2)
Histologic type — no. (%)		
Infiltrating ductal	1814 (76.8)	1871 (78.6)
Infiltrating lobular	346 (14.6)	327 (13.7)
Other	172 (7.3)	156 (6.6)
Unknown	3 (0.1)	1 (<0.1)
Missing data	27 (1.1)	25 (1.1)
Estrogen-receptor status — no. (%)†		
Positive	1917 (81.2)	1936 (81.3)
Progesterone-receptor positive	1312 (55.6)	1307 (54.9)
Progesterone-receptor negative	351 (14.9)	384 (16.1)
Progesterone-receptor status unknown or missing	254 (10.8)	245 (10.3)
Negative	26 (1.1)	33 (1.4)
Unknown	398 (16.9)	392 (16.5)
Missing data	21 (0.9)	19 (0.8)
Progesterone-receptor status — no. (%)		
Positive	1320 (55.9)	1313 (55.2)
Negative	360 (15.2)	395 (16.6)
Unknown	659 (27.9)	653 (27.4)
Missing data	23 (1.0)	19 (0.8)
Type of surgery — no. (%)		
Mastectomy	1222 (51.7)	1235 (51.9)
Breast-conserving	1116 (47.2)	1123 (47.2)
Unknown	3 (0.1)	2 (0.1)
Missing data	21 (0.9)	20 (0.8)
Previous chemotherapy — no. (%)		
Yes	766 (32.4)	765 (32.1)
No	1575 (66.7)	1596 (67.1)
Missing data	21 (0.9)	19 (0.8)
Previous hormone-replacement therapy — no. (%)		
Yes	567 (24.0)	557 (23.4)
No	1723 (72.9)	1747 (73.4)
Unknown	51 (2.2)	54 (2.3)
Missing data	21 (0.9)	22 (0.9)
Duration of tamoxifen therapy at randomization — yr		
Median	2.4	2.4
Interquartile range	2.1–2.7	2.1–2.7
Tamoxifen dose — no. (%)		
20 mg	2243 (95.0)	2270 (95.4)
30 mg	77 (3.3)	76 (3.2)
Missing data	42 (1.8)	34 (1.4)

* Plus–minus values are means ±SD. Patients with missing data had no value reported for a given variable; for patients in the “unknown” category, data were reported as unknown.

† Data for positive and negative estrogen-receptor status include retrospectively ascertained status for some patients whose status was unknown at randomization.

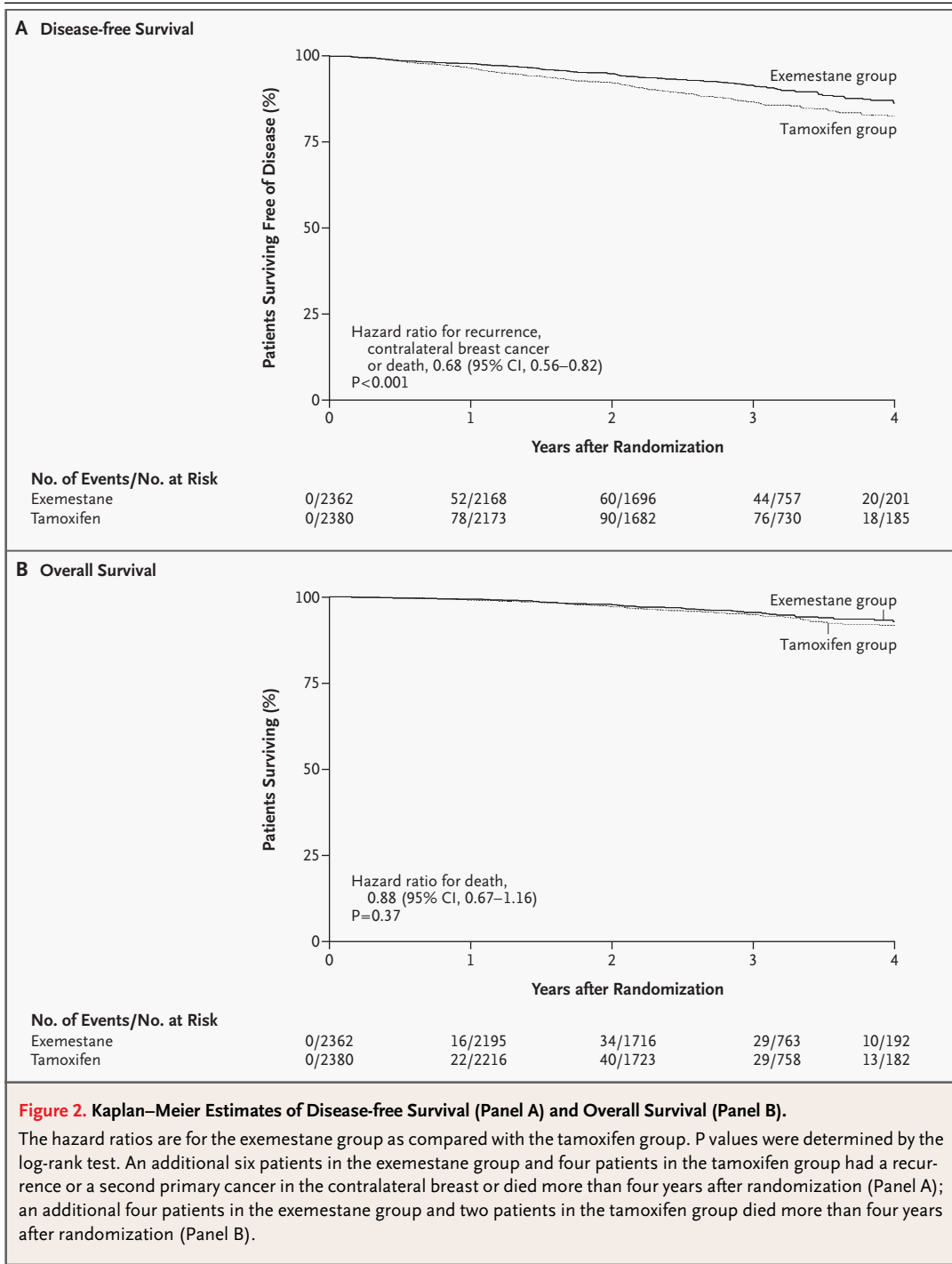
Table 2. End-Point Events.

Variable	Exemestane Group (N=2362)	Tamoxifen Group (N=2380)	All Patients (N=4742)
	<i>no. of patients</i>		
Events included in analysis of disease-free survival*			
Local recurrence only	21	33	54
Distant recurrence	114	174	288
Primary cancer in contralateral breast	9	20	29
Intercurrent death (without recurrence)	39	39	78
Recurrence, contralateral breast cancer, or intercurrent death	183	266	449
Death			
Any cause	93	106	199
Breast-cancer-related	54	67	121
Intercurrent (without recurrence)	39	39	78
Vascular causes	12	6	18
Cardiac causes	10	8	18
Other cancer-related	6	10	16
Thrombotic causes	1	1	2
Pulmonary causes	0	1	1
Other causes	6	7	13
Unknown causes or missing data	4	6	10
Second primary non-breast cancer	27	53	80
Lung	4	12	16
Gastrointestinal	7	10	17
Endometrial	5	11	16
Other gynecologic	3	3	6
Genitourinary	3	4	7
Melanoma	1	5	6
Lymphoreticular	2	3	5
Other	2	5	7

* Data for distant recurrence and primary cancer in the contralateral breast include patients who also reported a local relapse. One patient in the exemestane group died of breast cancer after contralateral breast cancer had been reported and is also included in the analysis of distant-disease-free survival.

to 0.82; $P=0.00005$ by the log-rank test), which corresponds to an absolute benefit of 4.7 percent (95 percent confidence interval, 2.6 to 6.8) at three years (Fig. 2). Disease-free survival three years after randomization was 91.5 percent (95 percent confidence interval, 90.0 to 92.7) in the exemestane group and 86.8 percent (95 percent confidence interval, 85.1 to 88.3) in the tamoxifen group. In a subsidiary analysis of breast-cancer-free survival in which deaths of patients who did not have a recurrence or contralateral breast cancer were censored, the hazard ratio was 0.63 (95 percent confidence interval, 0.51 to 0.77; $P=0.00001$; 144 events in the exemestane group vs. 227 in the tamoxifen group).

Survival free of distant disease was also better in the exemestane group (hazard ratio, 0.66; 95 percent confidence interval, 0.52 to 0.83; $P=0.0004$). A total of 199 patients have died (93 in the exemestane group and 106 in the tamoxifen group). There is no statistically significant difference in overall survival at this stage (hazard ratio, 0.88; 95 percent confidence interval, 0.67 to 1.16; $P=0.37$) (Fig. 2). The causes of death are listed in Table 2. Exemestane significantly reduced the risk of contralateral breast cancer (hazard ratio, 0.44; 95 percent confidence interval, 0.20 to 0.98; $P=0.04$).



Adjusting for the prespecified prognostic factors did not affect the hazard ratios (Table 3), and there was no evidence of heterogeneity among subgroups defined according to estrogen-receptor status, combined estrogen-receptor and progesterone-receptor status, number of positive nodes, receipt or type of previous chemotherapy,

or use at any time of hormone-replacement therapy (Fig. 3).

ADVERSE EFFECTS AND SAFETY

Exemestane was associated with a higher incidence of arthralgia and diarrhea than tamoxifen, but gynecologic symptoms, vaginal bleeding, and muscle

Table 3. Hazard Ratios in the Exemestane Group as Compared with the Tamoxifen Group.*

End Point	Unadjusted		Adjusted	
	Hazard Ratio (95% CI)	P Value	Hazard Ratio (95% CI)	P Value
Disease-free survival	0.68 (0.56–0.82)	<0.001	0.67 (0.56–0.82)	<0.001
Breast-cancer-free survival	0.63 (0.51–0.77)	<0.001	0.62 (0.50–0.76)	<0.001
Time to contralateral breast cancer	0.44 (0.20–0.98)	0.04	0.44 (0.20–0.98)	0.04
Overall survival	0.88 (0.67–1.16)	0.37	0.89 (0.67–1.17)	0.41

* A Cox model including estrogen-receptor status (either positive or negative, unknown or missing), nodal status (negative, 1 to 3 positive nodes, 4 or more positive nodes, or unknown or missing), chemotherapy (yes or no), and use of hormone-replacement therapy (yes, no, or unknown or missing) was used to estimate the adjusted hazard ratios. Forty patients with unknown chemotherapy status were excluded from the analysis. CI denotes confidence interval. P values were determined by the log-rank test.

cramps were more common with tamoxifen (Table 4). Thromboembolic events were recorded more frequently in the tamoxifen group than in the exemestane group (55 patients [2.4 percent] vs. 30 patients [1.3 percent], $P=0.007$). There was also a suggestion of an increased incidence of osteoporosis and visual disturbances associated with exemestane. Fractures were reported more frequently in the exemestane group than in the tamoxifen group, although the difference was not statistically significant (72 patients [3.1 percent] vs. 53 patients [2.3 percent], $P=0.08$). More patients in the tamoxifen group than in the exemestane group had a second primary non-breast cancer that occurred before a distant relapse (53 patients [2.2 percent] vs. 27 patients [1.1 percent]; hazard ratio, 0.51; 95 percent confidence interval, 0.32 to 0.80; $P=0.003$) (Table 2). Specifically, cancer of the endometrium, lung cancer, and melanoma developed in fewer patients in the exemestane group than in the tamoxifen group, although these individual differences were not statistically significant.

TREATMENT COMPLIANCE

Randomly assigned treatment was stopped early in 667 patients (365 in the exemestane group and 302 in the tamoxifen group; 14.1 percent of the total study population) for reasons other than relapse or death, after a median total duration of treatment of 36.1 months (from the initiation of tamoxifen therapy). A total of 138 patients in the exemestane group and 121 in the tamoxifen group discontinued ther-

apy because of adverse events, and another 164 patients in the exemestane group and 116 in the tamoxifen group refused to continue therapy. An additional 63 patients in the exemestane group and 65 in the tamoxifen group have discontinued their randomly assigned treatment for other reasons, including protocol violations, or have been lost to follow-up. On the basis of the time since randomization, 9 percent of patients are likely to be still receiving treatment.

DISCUSSION

We found that switching patients to adjuvant treatment with exemestane after two to three years of tamoxifen therapy was associated with a statistically and clinically significant improvement in disease-free survival, which included a reduction in the incidence of metastatic disease. This strategy also reduced the risks of contralateral breast cancer, endometrial cancer, and intriguingly, other primary cancers. At the time of this report, the observed number of deaths over the relatively short follow-up period precludes the detection of a statistically significant difference in overall survival.

The data and safety monitoring committee recommended the early release of results on the basis of a planned interim analysis. More than 90 percent of the patients will have completed their randomly assigned treatment by the time this report is published; thus, the trial should still be able to achieve its long-term assessment of survival benefit. There are several theoretical reasons to suggest a benefit of sequential endocrine therapy involving switching from tamoxifen to an aromatase inhibitor after two to three years. First, many patients with breast cancer have a relapse and die of metastatic disease within five years after the initial diagnosis. Second, in both patients with primary cancer and those with metastatic disease, resistance occurs as early as 12 to 18 months after the initiation of tamoxifen therapy. In some patients with resistant disease, tamoxifen may act as an agonist, potentially stimulating the division of breast-cancer cells. Third, serious side effects of tamoxifen, including thromboembolism and uterine carcinoma, can occur after prolonged use. Fourth, since tamoxifen can decrease bone resorption,²¹ we reasoned that pretreatment with tamoxifen might lessen the effect of any osteopenia caused by exemestane.

When we designed this study, there was considerable uncertainty regarding the optimal duration

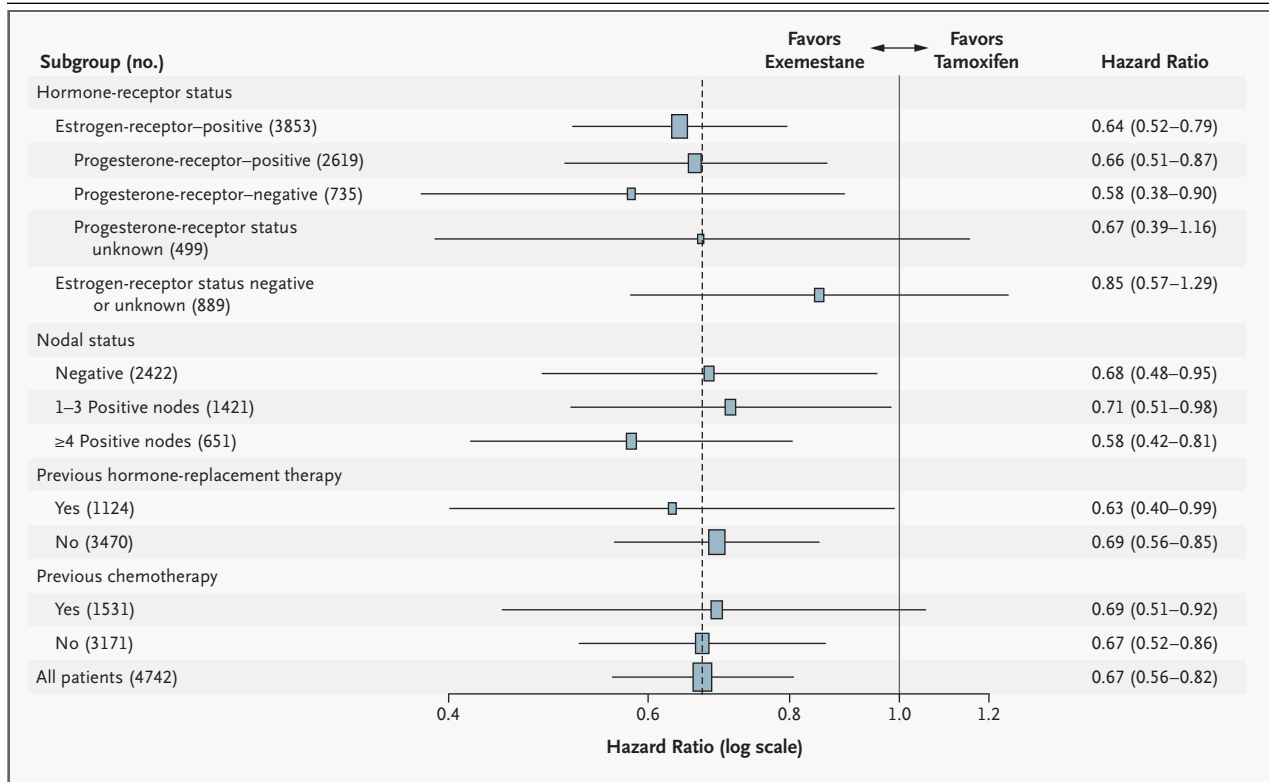


Figure 3. Subgroup Analysis of Disease-free Survival.

The hazard ratio given for all patients was adjusted for estrogen-receptor status, nodal status, receipt or nonreceipt of chemotherapy, and use or nonuse of hormone-replacement therapy ($P=0.00004$). The size of the rectangles is proportional to the size of the subgroups.

of adjuvant tamoxifen therapy in patients with primary breast cancer. The 1990 overview by the Early Breast Cancer Trialists' Collaborative Group had suggested that there was a likely benefit of continuing tamoxifen therapy for five years.²² Randomized trials directly comparing two years of tamoxifen therapy with five years of tamoxifen therapy^{23,24} confirmed that there was a relative risk reduction of 18 to 19 percent with the longer-term therapy. Thus, although five years of tamoxifen treatment was the identified standard, switching treatment after only two to three years was postulated to offer patients the bulk of the benefit of tamoxifen while minimizing the risk of long-term side effects.

Despite the promising results of the Anastrozole, Tamoxifen Alone or in Combination Trialists' Group (ATAC) study, which showed that anastrozole was superior to tamoxifen,²⁵ five years of tamoxifen therapy remains the widely recommended standard for adjuvant treatment,⁸ although the Food and Drug Administration recently approved anastrozole monotherapy as an alternative. A study by Goss et

al.¹⁹ found that after five years of tamoxifen therapy, patients who received letrozole had a higher rate of disease-free survival than those who received placebo. Our large, multicenter study challenges the concept of five years of monotherapy with endocrine agents after the surgical treatment of primary breast cancer. Two smaller studies conducted by Italian researchers have used sequential aminoglutethimide after tamoxifen therapy in 308 patients²⁶ and anastrozole after tamoxifen therapy in 426 patients.²⁷ Although they were underpowered, both trials suggested that the sequence may be better than tamoxifen alone, supporting the results we present here.

The improvement in disease-free survival achieved by switching from tamoxifen to exemestane is consistent with the hypothesis that breast cancer frequently becomes resistant to tamoxifen within five years after treatment is initiated. The molecular mechanisms underlying such resistance are unclear. Laboratory studies indicate that a reduction in the antagonist properties of tamoxifen caused by the up-regulation of tyrosine kinase receptors (in

Table 4. Adverse Events.*

Type of Event	Exemestane Group					Tamoxifen Group					P Value
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	
	number (percent)										
Cardiovascular disease other than myocardial infarction	984 (42.6)					913 (39.2)					0.016
Hot flashes	504	363	97	3	967 (42.0)	493	342	84	4	923 (39.6)	0.082
Pain or aches	392	305	61	8	766 (33.2)	383	242	55	4	684 (29.4)	0.001
Fatigue	336	178	31	0	545 (23.6)	352	157	36	2	547 (23.5)	0.776
Insomnia	269	143	37	0	449 (19.5)	234	140	31	1	406 (17.4)	0.151
Sweating	222	153	51	3	429 (18.6)	215	145	57	1	418 (17.9)	0.702
Headaches	272	129	26	1	428 (18.6)	243	116	17	2	378 (16.2)	0.035
Dizziness	206	73	9	0	288 (12.5)	192	74	13	0	279 (12.0)	0.904
Nausea	177	57	14	0	248 (10.8)	189	53	16	0	258 (11.1)	0.835
Visual disturbances	134	32	4	0	170 (7.4)	115	8	10	0	133 (5.7)	0.024
Osteoporosis	171 (7.4)					134 (5.7)					0.023
Gynecologic symptoms	135 (5.8)					211 (9.0)					<0.001
Arthralgia	124 (5.4)					85 (3.6)					0.005
Depression	68	50	2	0	120 (5.2)	51	37	5	0	93 (4.0)	0.114
Diarrhea	63	28	8	1	100 (4.3)	37	16	1	0	54 (2.3)	<0.001
Vaginal bleeding	49	33	11	0	93 (4.0)	73	50	5	1	129 (5.5)	0.087
Cramps	45	16	3	0	64 (2.8)	60	37	3	2	102 (4.4)	0.002
Thromboembolic disease	11	4	8	1	24 (1.0)	11	13	15	6	45 (1.9)	0.005
Including ungraded serious adverse events	30 (1.3)					55 (2.4)					0.007

* Data are given for adverse events whose incidence in the two groups differed by 1 percent or more, for which the difference between groups was significant at the 1 percent level, or whose incidence was at least 10 percent in either group. Grades are according to Common Toxicity Criteria of the National Cancer Institute (version 1.0). Data on cardiovascular disease, gynecologic symptoms, osteoporosis, and arthralgia were available for 2309 patients in the exemestane group and 2332 patients in the tamoxifen group; data on the other adverse effects were available for 2305 and 2329 patients, respectively. Pain or aches, arthralgia, depression, diarrhea, and cramps were recorded in an "other" category; data are preliminary and may underestimate the true incidence. For graded adverse events, P values were determined by trend tests combining grades 3 and 4.

particular, HER2 and epidermal growth-factor receptors), downstream protein kinases (such as mitogen-activated protein kinase²⁸ and protein kinase B, or Akt²⁹), or both may result in a significant increase in the agonist activity of tamoxifen, as well as increased sensitivity to estradiol. These effects could explain the benefit that has been observed to result from lowering the estradiol level through the sequential use of an aromatase inhibitor.⁹

Results in the subgroup with estrogen-receptor-positive breast cancer were very similar to those among all patients. According to an unplanned subgroup analysis, exemestane seemed to be equally effective in both progesterone-receptor-positive and progesterone-receptor-negative subgroups, as well as in node-positive and node-negative subgroups,

contrary to the report suggesting that patients with estrogen-receptor-positive and progesterone-receptor-negative carcinomas may preferentially benefit from anastrozole therapy.³⁰

The reduction in the incidence of contralateral breast cancer in the exemestane group as compared with the tamoxifen group (hazard ratio, 0.44; 95 percent confidence interval, 0.20 to 0.98; P=0.04) suggests that preventive strategies involving the prolonged use of tamoxifen monotherapy^{31,32} may not be optimal. The nonsignificant decrease in the rate of endometrial cancer is consistent with expectations, since tamoxifen therapy is a well-recognized risk factor for endometrial cancer.^{33,34} The decreased incidence of other second primary (non-breast) cancers is more difficult to explain.

Reports of associations between tamoxifen therapy and cancer at other sites have been inconclusive,³⁴ and such associations were not substantiated by the Early Breast Cancer Trialists' Collaborative Group study.⁵ Thus, it is not clear whether the observed differences in the incidence of new primary cancers represent increases in risks due to tamoxifen treatment, a previously unreported protective effect of an aromatase inactivator, or chance findings.

The rate of discontinuation of treatment was slightly higher in the exemestane group than in the tamoxifen group, perhaps reflecting differences in the side-effect profiles of the two treatments that may have been particularly evident to patients switching from one treatment to another. The analysis of adverse events indicated that there was a lower incidence of thromboembolic events among women who switched to exemestane. There was a slight but nonsignificant increase in the rate of osteoporosis and reported fractures in the exemestane group as compared with the tamoxifen group. Recent studies have shown that all third-generation aromatase inhibitors or inactivators increase bone resorption.^{35,36} The substudy of the IES on bone mineral density aims to determine the degree of bone mineral loss in patients who have been treated with tamoxifen and then switched to exemestane. The increase in the rate of arthralgia in the exemestane group is similar to that seen with other aromatase inhibitors,³⁷ and diarrhea has been reported previously in patients receiving exemestane.¹⁶ Cholesterol levels, which were reduced by tamoxifen treatment,³⁸ were found to be unaltered in another study of exemestane³⁹ but were not systematically measured in the present study; we have not observed a significantly increased incidence of myocardial infarction (1.0 percent in the exemestane group vs. 0.4 percent in the tamoxifen group).

Several issues still need to be clarified, including the correct sequence of therapy, which we believe to be an important factor in the success of this study and that reported by Goss et al.,¹⁹ as well as the effect of aromatase inhibition on bone metabolism.

The answers to these questions will have to await the results of ongoing and new studies. Our results add to the evidence that the sequential use of aromatase inactivators and tamoxifen provides additional options for improving adjuvant endocrine therapy for postmenopausal women with hormone-responsive primary breast cancer. Our results indicate that five years of tamoxifen monotherapy after surgery may be suboptimal for postmenopausal patients with estrogen-receptor-positive breast cancer and suggest that clinicians should consider switching patients to exemestane between two and three years after the start of tamoxifen therapy.

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