

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

NOVEMBER 6, 2003

VOL. 349 NO. 19

A Randomized Trial of Letrozole in Postmenopausal Women after Five Years of Tamoxifen Therapy for Early-Stage Breast Cancer

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ABSTRACT

BACKGROUND

In hormone-dependent breast cancer, five years of postoperative tamoxifen therapy — but not tamoxifen therapy of longer duration — prolongs disease-free and overall survival. The aromatase inhibitor letrozole, by suppressing estrogen production, might improve the outcome after the discontinuation of tamoxifen therapy.

METHODS

We conducted a double-blind, placebo-controlled trial to test the effectiveness of five years of letrozole therapy in postmenopausal women with breast cancer who have completed five years of tamoxifen therapy. The primary end point was disease-free survival.

RESULTS

A total of 5187 women were enrolled (median follow-up, 2.4 years). At the first interim analysis, there were 207 local or metastatic recurrences of breast cancer or new primary cancers in the contralateral breast — 75 in the letrozole group and 132 in the placebo group — with estimated four-year disease-free survival rates of 93 percent and 87 percent, respectively, in the two groups ($P \leq 0.001$ for the comparison of disease-free survival). A total of 42 women in the placebo group and 31 women in the letrozole group died ($P = 0.25$ for the comparison of overall survival). Low-grade hot flashes, arthritis, arthralgia, and myalgia were more frequent in the letrozole group, but vaginal bleeding was less frequent. There were new diagnoses of osteoporosis in 5.8 percent of the women in the letrozole group and 4.5 percent of the women in the placebo group ($P = 0.07$); the rates of fracture were similar. After the first interim analysis, the independent data and safety monitoring committee recommended termination of the trial and prompt communication of the results to the participants.

CONCLUSIONS

As compared with placebo, letrozole therapy after the completion of standard tamoxifen treatment significantly improves disease-free survival.

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This article was published at www.nejm.org on October 9, 2003.

N Engl J Med 2003;349:1793-802.

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THE RISK OF A RECURRENCE OF BREAST cancer continues for an indefinite period after surgery, radiation, and medical therapy.^{1,2} Since the growth of breast cancer depends on the action of estrogen,³ long-term reductions in the risk of recurrence have been achieved by antagonizing the activity of estrogen with the selective estrogen-receptor modulator tamoxifen in women with hormone-receptor–positive tumors.^{1,2} The postoperative administration of tamoxifen for five years reduces the risk of recurrence by 47 percent and reduces the risk of death by 26 percent.^{2,4} However, in a trial conducted by the National Surgical Adjuvant Breast and Bowel Project (NSABP), women who continued to receive tamoxifen therapy after five years had worse outcomes than women in whom it was discontinued at five years.^{5,6} On the basis of these results, the National Cancer Institute has recommended that, outside of a clinical trial, tamoxifen treatment should be limited to five years.⁷

Tamoxifen is both an antagonist and a partial agonist of the estrogen receptor.⁸ Over time, its agonist action may become exaggerated and thereby impair its potential anticancer activity. It is known that resistance to tamoxifen and dependence on its estrogen-agonist effects develop in breast-cancer cells that are cultured in the presence of tamoxifen.^{9–17} In women with metastatic disease that progresses despite tamoxifen therapy, aromatase (estrogen synthetase) inhibitors, including letrozole, have demonstrated efficacy.^{18,19}

In this study of postmenopausal women who had been treated for early-stage breast cancer, we investigated whether letrozole would have antitumor effects after 4.5 to 6 years of tamoxifen therapy had been completed. We report the results of our first planned interim analysis. After reviewing the information presented here, the data and safety monitoring committee recommended that, in the interest of patient care, the study be discontinued early, and the participants informed of the results. These actions were taken immediately before this article was published.

METHODS

STUDY DESIGN

We conducted a phase 3, randomized, double-blind, placebo-controlled trial of letrozole in postmenopausal women with primary breast cancer who had completed approximately 5 years (range, 4.5 to 6) of adjuvant tamoxifen therapy. Women were randomly

assigned to receive letrozole (2.5 mg) or placebo orally daily for five years. Women were stratified according to the tumor hormone-receptor status (positive or unknown), lymph-node status (negative, positive, or unknown), and receipt or nonreceipt of previous adjuvant chemotherapy. The primary end point was disease-free survival, defined as the time from randomization to the recurrence of the primary disease (in the breast, chest wall, or nodal or metastatic sites) or the development of a new primary breast cancer in the contralateral breast. Secondary cancer and death without a recurrence or a diagnosis of contralateral breast cancer were not included as events in this analysis.

The secondary end points included overall survival (defined as the time to death from any cause), quality of life, and long-term safety. Adverse events were assessed according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0). Quality of life was assessed by means of the Medical Outcomes Study 36-Item Short Form General Health Survey (SF-36) and the Menopause-Specific Quality of Life (MENQOL) questionnaire.^{20,21} Companion studies assessed the lipid profile and the bone mineral density annually.

The institutional review board of each participating institution approved the study protocol. All patients gave written informed consent.

STUDY POPULATION

Women were eligible if they were at least 50 years of age at the start of adjuvant tamoxifen therapy, if they were younger than 50 years but were postmenopausal at the initiation of tamoxifen therapy, if they were younger than 50 years at the start of tamoxifen therapy but had undergone bilateral oophorectomy, if they were premenopausal and younger than 50 years of age at the start of tamoxifen therapy but became amenorrheic during chemotherapy or treatment with tamoxifen, or if they had postmenopausal levels of luteinizing hormone or follicle-stimulating hormone. Other criteria for eligibility included the following: previous adjuvant tamoxifen therapy lasting 4.5 to 6 years; histologically confirmed primary breast cancer; a tumor that was positive for estrogen receptors, progesterone receptors, or both (defined by a level of 10 fmol per milligram of protein or a positive result on immunohistochemical analysis or estrogen-receptor or progesterone-receptor immunocytochemical analysis); discontinuation of tamoxifen therapy less than 3 months before enrollment; an Eastern Cooperative Oncology Group perform-

ance status of 0, 1, or 2 (scored on a scale of 0 to 5, with lower scores indicating better function); and a life expectancy of more than 5 years. Imaging studies were performed to rule out metastatic disease only in women who were symptomatic or had abnormal blood tests.

Criteria for exclusion were the concurrent use of investigational drugs and a history of or the presence of another type of cancer other than skin cancer or carcinoma in situ of the cervix. Concomitant systemic hormone-replacement therapy or concomitant treatment with a selective estrogen-receptor modulator was contraindicated. Intermittent treatment with vaginal estrogens was permitted.

STUDY PROCEDURES

Women were randomly assigned to treatment groups with the use of the minimization method.²² They were assessed at one month, through telephone interviews, for compliance and toxic effects. Clinical evaluation, routine blood work, and evaluation of toxic effects were performed semiannually during year 1 and annually thereafter; mammography was performed annually throughout the study. At base line, women reported previous diagnoses of bone fractures, osteoporosis, or cardiovascular disease. Subsequently, new diagnoses were reported by women at follow-up visits. Treatment was discontinued if there was serious intercurrent illness, unacceptable toxic effects, or a recurrence of disease or at the request of the patient. SF-36 and MENQOL questionnaires were completed by a subgroup of women. Recurrence of disease was defined pathologically or on the basis of clinical or radiologic findings, and recurrences were dated at the time they were first detected.

Interim safety analyses were reviewed twice yearly by the data and safety monitoring committee. Funding was provided by the Canadian Cancer Society, the U.S. National Cancer Institute, and Novartis Pharmaceuticals. Data were collected, managed, and analyzed by the National Cancer Institute of Canada Clinical Trials Group. The trial committee made the decision to publish the results.

STATISTICAL ANALYSIS

The sample size was calculated under the assumptions of a four-year disease-free survival rate of 88 percent in the placebo group and the detection of a difference of 2.5 percent in the four-year disease-free survival rate (hazard ratio for local or metastatic recurrence of the disease or the diagnosis of con-

tralateral breast cancer, 0.78), with 80 percent power at a two-sided alpha level of 0.05. These assumptions necessitated the enrollment of 4800 women over a four-year period with two years of follow-up, accounting for 515 events.

Two interim analyses were to be conducted, after 171 and 342 events had occurred. Early termination would be considered at the time of the interim analyses if the P value of the stratified log-rank test was below a nominal significance level calculated with the use of the Lan-DeMets alpha spending function, with O'Brien-Fleming boundaries that maintained the overall significance of the study at a two-sided alpha level of 0.05.²³

The required minimal number of events for the first interim analysis (171) had occurred by March 2003. This report is based on the results presented to the data and safety monitoring committee on August 22, 2003; it includes data on efficacy through August 19, 2003, and data on adverse events through February 28, 2003. Disease-free survival and overall survival were the two efficacy end points considered in the interim analysis. For the analysis of disease-free survival, data for the women who died without a recurrence of breast cancer or a new diagnosis of contralateral primary breast cancer were censored at the date of death. The stratified log-rank test, taking into account the stratification factors used for randomization, was used for the comparison of the treatment groups in terms of disease-free and overall survival.²⁴ The chi-square test was used for the comparison of the groups in terms of the rates of toxic effects. All reported P values are two-sided.

RESULTS

STUDY POPULATION

Between August 1998 and September 2002, 5187 women underwent randomization; 2593 were assigned to the letrozole group, and 2594 to the placebo group. In order to complete accrual to a substudy focused on effects on bone, enrollment exceeded the planned 4800 women. Thirty women (18 in the letrozole group and 12 in the placebo group) who did not have investigation forms at base line were excluded from the analyses. Thirty-nine women (19 in the letrozole group and 20 in the placebo group) were deemed ineligible because they had received adjuvant tamoxifen therapy for too long, too much time had elapsed since their discontinuation of such therapy, their menopausal status did not meet the

Table 1. Base-Line Characteristics of the 5157 Postmenopausal Women Included in the Analysis.*

Characteristic	Letrozole Group (N=2575)	Placebo Group (N=2582)
Menopausal status — no. (%)		
Missing data	8 (<1)	4 (<1)
≥50 yr of age	1958 (76)	1953 (76)
<50 yr of age, considered postmenopausal	177 (7)	146 (6)
<50 yr of age, underwent bilateral oophorectomy	91 (4)	101 (4)
<50 yr of age, became amenorrheic	327 (13)	364 (14)
Postmenopausal levels of luteinizing hormone or follicle-stimulating hormone	14 (1)	14 (1)
Age at enrollment		
Missing data — no. (%)	6 (<1)	1 (<1)
≤39 Yr — no. (%)	10 (<1)	5 (<1)
40–49 Yr — no. (%)	193 (7)	207 (8)
50–59 Yr — no. (%)	855 (33)	875 (34)
60–69 Yr — no. (%)	829 (32)	855 (33)
≥70 Yr — no. (%)	682 (26)	639 (25)
Median age — yr	62.4	62.0
Previous adjuvant radiation therapy — no. (%)		
Missing data	12 (<1)	5 (<1)
No	1012 (39)	1047 (41)
Yes	1550 (60)	1528 (59)
Unknown	1 (<1)	2 (<1)
Previous adjuvant chemotherapy — no. (%)		
Missing data	7 (<1)	1 (<1)
No	1393 (54)	1404 (54)
Yes	1175 (46)	1177 (46)
Type of surgery — no. (%)		
Lumpectomy	1451 (56)	1466 (57)
Mastectomy	1286 (50)	1301 (50)
Axillary-node dissection	2428 (94)	2447 (95)

eligibility criteria, they had had a previous recurrence, they currently had or had previously had another type of cancer, their primary surgery had been inadequate, they had a hormone-receptor-negative tumor, they had inadequate investigations at base line, or they were receiving simultaneous hormone therapy. These women were included in the analysis according to the intention-to-treat principle. The two groups were balanced in terms of all relevant base-line characteristics (Table 1).

STUDY OUTCOME

At a median follow-up of 2.4 years in this first analysis, 207 events (40 percent of the events required for the final analysis) had occurred. With this num-

ber of events, the O'Brien–Fleming boundary was 0.0008. Figure 1A shows the Kaplan–Meier curves for disease-free survival in the two groups. The estimated four-year disease-free survival rate was 93 percent in the letrozole group and 87 percent in the placebo group. The hazard ratio for a local or metastatic recurrence or new contralateral breast cancer in the letrozole group as compared with the placebo group was 0.57 (95 percent confidence interval, 0.43 to 0.75; $P=0.00008$). We also performed a sensitivity analysis in which we counted the deaths of women who did not have a recurrence or contralateral breast cancer as events in the estimation of disease-free survival, instead of censoring the data for these women. In this analysis, the hazard ratio for death,

Table 1. (Continued.)

Characteristic	Letrozole Group (N=2575)	Placebo Group (N=2582)
Axillary nodal status — no. (%)		
Missing data	7 (<1)	1 (<1)
Negative	1291 (50)	1290 (50)
Positive	1175 (46)	1195 (46)
Unknown	102 (4)	96 (4)
Receptor status — no. (%)		
Missing data	8 (<1)	2 (<1)
Positive	2518 (98)	2530 (98)
Unknown	49 (2)	50 (2)
Previous diagnosis of bone fracture — no. (%)		
Missing data	5 (<1)	2 (<1)
No	2276 (88)	2270 (88)
Yes	288 (11)	307 (12)
Unknown	6 (<1)	3 (<1)
Previous diagnosis of osteoporosis — no. (%)		
Missing data	10 (<1)	5 (<1)
No	2260 (88)	2278 (88)
Yes	304 (12)	297 (12)
Unknown	1 (<1)	2 (<1)
Previous diagnosis of cardiovascular disease — no. (%)		
Missing data	8 (<1)	5 (<1)
No	2256 (88)	2292 (89)
Yes	311 (12)	284 (11)
Unknown	0	1 (<1)

* "Missing data" are data that were not reported; "unknown" represents data that were reported as unknown.

recurrence, or contralateral breast cancer in the letrozole group as compared with the placebo group was 0.61 (95 percent confidence interval, 0.47 to 0.79; $P < 0.001$).

In an unplanned subgroup analysis, the effect of letrozole was at least as great among women with node-negative disease (hazard ratio for recurrence or contralateral breast cancer, 0.47; $P = 0.005$) as among those with node-positive disease (hazard ratio, 0.60; $P = 0.003$). Table 2 shows the sites of recurrence; there were fewer locoregional and distant recurrences and fewer new primary tumors in the contralateral breast in the letrozole group than in the placebo group.

Among the 25 women who had only local recurrences in the ipsilateral breast, 4 had ductal or lobular carcinoma in situ (all in the placebo group), and

among the 40 women in whom new primary tumors developed in the contralateral breast, 6 had ductal or lobular carcinoma in situ (1 in the letrozole group and 5 in the placebo group). Seventy-three deaths have been reported (31 in the letrozole group and 42 in the placebo group) (Table 3 and Fig. 1B). The estimated four-year overall survival rate was 96 percent in the letrozole group and 94 percent in the placebo group. The hazard ratio for death from any cause in the letrozole group as compared with the placebo group was 0.76 (95 percent confidence interval, 0.48 to 1.21; $P = 0.25$). Table 4 shows the rates of disease-free survival and overall survival through year 4.

SAFETY

Table 5 shows data on safety and toxic effects in the first 4299 women enrolled in the study. Toxic effects

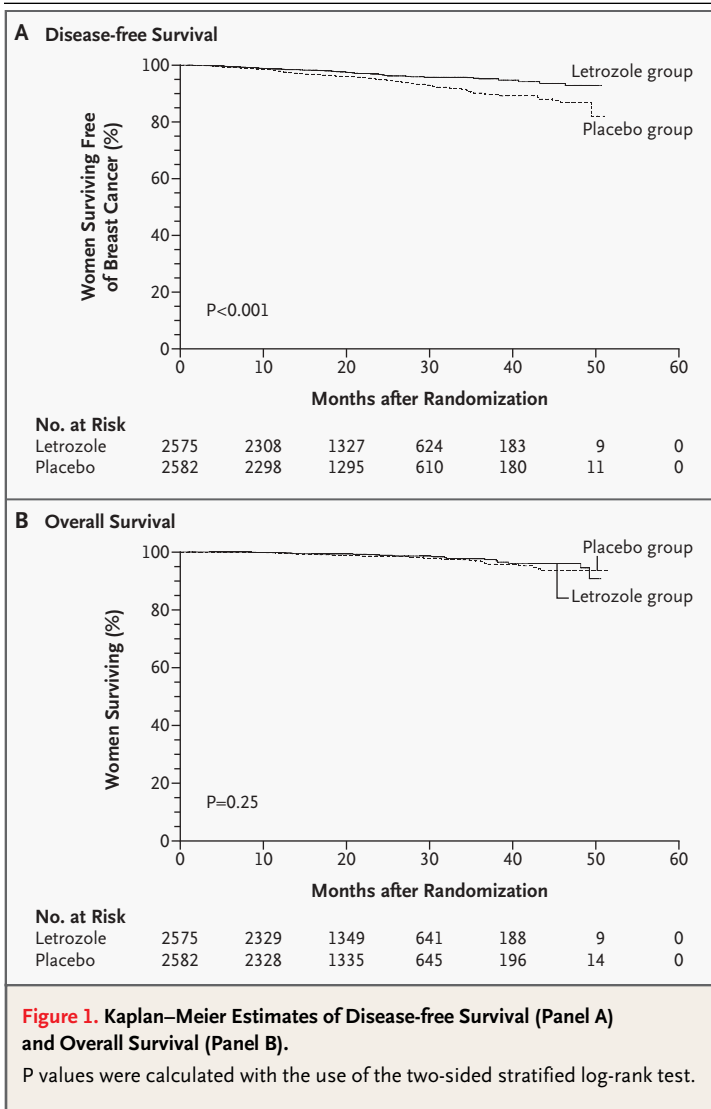


Table 2. Recurrences of Primary Cancers and New Contralateral Breast Cancers.

Variable	Letrozole Group (N=2575)	Placebo Group (N=2582)
	<i>no. (%)</i>	
Recurrence*	61 (2.4)	106 (4.1)
Local, ipsilateral breast only	6	19
Local, ipsilateral chest wall only	2	7
Regional nodes only	6	4
Distant site or sites†	47	76
Bone marrow	4	4
Lungs	9	14
Bone	29	44
Pleural effusion	0	8
Liver	14	13
Central nervous system	0	2
Other	11	18
New primary tumor in the contralateral breast only	14 (0.5)	26 (1.0)
Total with recurrence or new contralateral breast cancer	75	132

* Data are for women with a recurrence of the primary cancer, with or without contralateral breast cancers.
† Some women had a distant recurrence at more than one site.

more women in the letrozole group had at least one cardiovascular event or new bone fracture, but neither difference between the groups was significant (P=0.40 and P=0.24, respectively).

DISCUSSION

were primarily of grade 1 or 2. Hot flashes, arthritis, arthralgia, and myalgia were more common in the letrozole group than in the placebo group (P<0.05 for all comparisons). Vaginal bleeding was more common in the placebo group (P=0.01). A total of 4.5 percent of the women in the letrozole group discontinued the study treatment because of toxic effects, as compared with 3.6 percent of the women in the placebo group; the difference was not significant (P=0.11). Approximately equal numbers of women in the letrozole group (256) and the placebo group (254) chose to discontinue treatment.

There was a trend toward a higher rate of reports of newly diagnosed osteoporosis in the letrozole group than in the placebo group (P=0.07). Slightly

We compared therapy with letrozole, an aromatase inhibitor, with a placebo in healthy women with previously treated early breast cancer. The study treatment was given from years 5 through 10 after the diagnosis—a period when further tamoxifen therapy is not beneficial but when relapses of breast cancer occur.^{5,6} Several other trials comparing aromatase inhibitors with tamoxifen as adjuvant therapy for the first five years after diagnosis or studying aromatase inhibitors used in sequence with tamoxifen are under way.²⁵ Preliminary results from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial show that disease-free survival is longer with anastrozole than with tamoxifen,²⁶ although tamoxifen therapy is still considered an acceptable standard of care.^{27,28}

Table 3. Causes of Death.*

Cause	Letrozole Group (N=2575)	Placebo Group (N=2582)
	no.	
Breast cancer	9	17
Other primary cancer	4	4
Other condition or circumstance	17	21
Unknown	1	0

* Causes were reported by participating investigators.

We found a significant improvement in disease-free survival, including a substantial reduction in the rate of distant metastasis in the letrozole group as compared with the placebo group; the rate of death due to breast cancer was almost halved. Letrozole was equally effective in women with node-negative disease and those with node-positive disease. The reduction in the rates of recurrent and new disease in the letrozole group confirms the continuous dependence of hormone-receptor-positive breast cancer on estrogen.

The data and safety monitoring committee concluded that the results concerning disease-free survival would in themselves have necessitated the unblinding of the study. In addition, the trend toward a reduction in overall mortality in the letrozole group, albeit not statistically significant, influenced the members of the committee to recommend that this information be made available expeditiously. This step was taken immediately before the publication of this article.

The reduction in the frequency of new primary tumors in the contralateral breast (a relative reduction of 46 percent), a secondary end point of our trial, is compatible with the reduction in the frequency of contralateral disease among women who received adjuvant tamoxifen therapy in earlier studies,² as well as the reductions among women in the NSABP tamoxifen prevention trial²⁹ and those in the ATAC trial.²⁶

Tamoxifen provides protection against bone fractures and lowers serum cholesterol levels.³⁰⁻³² In contrast, aromatase inhibitors, by decreasing estrogen levels, may reduce bone mineral density and cause hypercholesterolemia. Studies of the effects of letrozole on plasma lipids have had conflicting results.^{33,34} We found a nonsignificant difference in the rate of cardiovascular events between the letro-

Table 4. Disease-free and Overall Survival in Years 1 through 4.

Variable	Letrozole Group (N=2575)	Placebo Group (N=2582)	Absolute Difference (95% CI)*
	%		
Disease-free survival			
Yr 1	98.6	97.8	0.8 (0.0 to 1.5)
Yr 2	96.7	94.8	1.9 (0.6 to 3.3)
Yr 3	95.2	90.2	5.0 (2.7 to 7.3)
Yr 4	92.8	86.8	6.0 (2.0 to 10.1)
Overall survival			
Yr 1	99.8	99.7	0.1 (-0.2 to 0.4)
Yr 2	98.9	98.6	0.3 (-0.5 to 1.1)
Yr 3	97.7	96.9	0.8 (-0.8 to 2.3)
Yr 4	96.0	93.6	2.4 (-0.9 to 5.6)

* CI denotes confidence interval.

zole group (4.1 percent) and the placebo group (3.6 percent), and there were no reports of drug-related hypercholesterolemia. Longer follow-up is needed to rule out the possibility that letrozole has adverse cardiovascular effects. Ongoing monitoring for toxic effects in women receiving letrozole therapy and analysis of our lipid substudy are planned.

Estrogen deficiency is associated with menopausal osteoporosis.³⁵ Both anastrozole and letrozole have been shown to increase bone resorption,^{26,36,37} but they have not been associated with osteoporosis. In our study, more women in the letrozole group than in the placebo group reported diagnoses of new-onset osteoporosis, and fractures occurred in a few more women in the letrozole group than in the placebo group (3.6 percent and 2.9 percent, respectively). Because of the early discontinuation of our study, however, these data may underestimate the long-term effects of letrozole on bone metabolism. The effectiveness of adding bisphosphonates to aromatase inhibitors is under evaluation. Until the results of this evaluation become available, we recommend that women receiving long-term letrozole therapy take calcium and vitamin D according to the guidelines for the prevention of osteoporosis and that their physicians consider monitoring their bone mineral density.

Hot flashes, arthritis, arthralgia, and myalgia, although more common with letrozole, were generally low-grade. Few women discontinued the study treatment because of toxic effects. The consequences of these effects should be clarified by analyses

Table 5. Adverse Events during the Study.*

Adverse Event	Letrozole Group (N=2154)					Placebo Group (N=2145)					P Value
	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Any Grade	
	number (percent)					number (percent)					
Edema	305	62	3	0	370 (17.2)	267	65	2	1	335 (15.6)	0.17
Hot flashes	636	380	0	0	1016 (47.2)	552	317	0	0	869 (40.5)	<0.001
Fatigue	520	112	11	0	643 (29.9)	477	125	5	0	607 (28.3)	0.26
Sweating	360	116	0	0	476 (22.1)	323	122	0	0	445 (20.7)	0.28
Constipation	185	35	4	0	224 (10.4)	169	45	2	0	216 (10.1)	0.72
Vaginal bleeding	75	15	2	0	92 (4.3)	92	32	2	2	128 (6.0)	0.01
Arthritis	86	27	6	1	120 (5.6)	57	17	1	0	75 (3.5)	<0.001
Hypercholesterolemia	237	19	1	0	257 (11.9)	215	28	4	0	247 (11.5)	0.67
Clinical fractures					77 (3.6)					63 (2.9)	0.24
Cardiovascular events					88 (4.1)					77 (3.6)	0.40
Osteoporosis					124 (5.8)					97 (4.5)	0.07
Dizziness	218	36	5	0	259 (12.0)	207	33	5	0	245 (11.4)	0.54
Headache	301	74	14	0	389 (18.1)	306	80	12	1	399 (18.6)	0.65
Arthralgia	274	164	21	0	459 (21.3)	218	123	14	0	355 (16.6)	<0.001
Myalgia	160	81	13	0	254 (11.8)	134	61	9	0	204 (9.5)	0.02

* Data are for adverse events whose incidence in the two groups differed by more than 1 percent or whose incidence was at least 10 percent in either group. Grades are according to the Common Toxicity Criteria of the National Cancer Institute, version 2.0. Data on clinical fractures, cardiovascular events, and osteoporosis were available for 2166 women in the letrozole group and 2157 women in the placebo group.

of our data on quality of life, but because of the early termination of our study, we could not present these data here. Endometrial cancer is in part an estrogen-dependent cancer and represents a rare complication of tamoxifen therapy that may occur even after the discontinuation of treatment with the drug.^{29,38,39} Vaginal bleeding was significantly less frequent in the letrozole group than in the placebo group in our study, and future studies to determine whether letrozole reduces the risk of endometrial cancer will be of interest.

Letrozole therapy resulted in a significant improvement in disease-free survival, which included a reduction in the frequency of new primary tumors in the contralateral breast; this reduction accounted for 21 percent of the difference in events between the treatment groups (12 of 57 events). The rates of distant recurrence of disease and death due to breast cancer were also lower in the letrozole group than in the placebo group.

On the basis of these findings, postmenopausal women with hormone-receptor-positive tumors who have completed about five years of adjuvant ta-

moxifen therapy should be considered for letrozole treatment. However, our results, which necessitated the discontinuation of the study, leave the optimal duration of treatment undefined and the question of long-term toxicity unanswered. Data from other, ongoing aromatase-inhibitor trials will contribute information regarding toxic effects, but the question of the optimal duration of treatment will not be answered by the current trials. Our study did not address the efficacy of letrozole therapy in women in whom tamoxifen therapy had been discontinued more than three months earlier, but because there was an ongoing reduction in the hazard of recurrence in the letrozole group, the use of the drug in such women should be considered. Consequently, our trial committee has recommended that women in the placebo group in our study discuss their personal risk profile with their oncologist and be considered for letrozole therapy. Our results do not apply to premenopausal women, since therapy with aromatase inhibitors alone does not suppress estrogen production adequately in women who are still ovulating.⁴⁰ These results show that in postmeno-

pausal women, letrozole therapy significantly improves disease-free survival.

Supported by the Canadian Cancer Society through a grant (no. 10362) from the National Cancer Institute of Canada, by grants (CA31946, CA21115, CA25224, CA38926, and CA32102) from the National Cancer Institute of the United States, and by Novartis Pharmaceuticals.

Drs. Goss, Ingle, Piccart, and Norton report having received consulting fees from Novartis; Drs. Goss, Ingle, and Piccart report having received lecture fees from Novartis; and Drs. Shepherd, Pritchard, Perez, Therasse, and Pater report having received research support from Novartis.

We are indebted to the women who participated in this study; to the trial committee; to the investigators, pharmacists, and clinical research associates from the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG), the Southwest Oncology Group, the Eastern Cooperative Oncology Group, the Cancer and Leukemia Group B, the North Central Cancer Treatment Group, the European Organization for Research and Treatment of Cancer, the International Breast Cancer Study Group, and centers in England including the Royal Marsden, St. George's, and the Withington Hospitals; to the members of the data safety and monitoring committee; and to the central office staff of the NCIC CTG who contributed to the conduct of the trial.

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