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A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer

The Breast International Group (BIG) 1-98 Collaborative Group*

ABSTRACT

BACKGROUND

The aromatase inhibitor letrozole is a more effective treatment for metastatic breast cancer and more effective in the neoadjuvant setting than tamoxifen. We compared letrozole with tamoxifen as adjuvant treatment for steroid-hormone-receptor–positive breast cancer in postmenopausal women.

METHODS

The Breast International Group (BIG) 1-98 study is a randomized, phase 3, double-blind trial that compared five years of treatment with various adjuvant endocrine therapy regimens in postmenopausal women with hormone-receptor–positive breast cancer: letrozole, letrozole followed by tamoxifen, tamoxifen, and tamoxifen followed by letrozole. This analysis compares the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially; events and follow-up in the sequential-treatment groups were included up to the time that treatments were switched.

RESULTS

A total of 8010 women with data that could be assessed were enrolled, 4003 in the letrozole group and 4007 in the tamoxifen group. After a median follow-up of 25.8 months, 351 events had occurred in the letrozole group and 428 events in the tamoxifen group, with five-year disease-free survival estimates of 84.0 percent and 81.4 percent, respectively. As compared with tamoxifen, letrozole significantly reduced the risk of an event ending a period of disease-free survival (hazard ratio, 0.81; 95 percent confidence interval, 0.70 to 0.93; P=0.003), especially the risk of distant recurrence (hazard ratio, 0.73; 95 percent confidence interval, 0.60 to 0.88; P=0.001). Thromboembolism, endometrial cancer, and vaginal bleeding were more common in the tamoxifen group. Women given letrozole had a higher incidence of skeletal and cardiac events and of hypercholesterolemia.

CONCLUSIONS

In postmenopausal women with endocrine-responsive breast cancer, adjuvant treatment with letrozole, as compared with tamoxifen, reduced the risk of recurrent disease, especially at distant sites. (ClinicalTrials.gov number, NCT00004205.)

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Adjuvant endocrine therapy with tamoxifen significantly prolongs disease-free and overall survival in postmenopausal women with early-stage breast cancer. Five years of treatment with tamoxifen reduces the risk of breast-cancer recurrence by 47 percent and the risk of death by 26 percent among patients with hormone-receptor–positive breast cancer.[1] Despite these benefits, about half the women so treated relapse. Tamoxifen treatment is associated with rare but serious adverse effects, including endometrial cancer and thromboembolism.[1]

In contrast to tamoxifen, which inhibits the activity of estrogen by competitively binding to the estrogen receptor, aromatase inhibitors block the conversion of androgens to estrogens and reduce estrogen levels in tissue and plasma.[2,3] Third-generation aromatase inhibitors include the nonsteroidal inhibitors letrozole and anastrozole and the steroidal inhibitor exemestane. With daily oral administration, anastrozole and exemestane inhibit aromatase activity in vivo by 97 to 98 percent and letrozole inhibits aromatase by more than 99 percent.[4-7]

As first-line treatment for metastatic breast cancer, third-generation aromatase inhibitors are equivalent or superior to tamoxifen.[3] Women with metastatic breast cancer who were given letrozole as first-line treatment had a significantly higher response rate, a significantly longer time to progression, and a significant improvement in one- and two-year survival rates, as compared with women given tamoxifen.[8,9] Among women with early-stage breast cancer who were free of disease after five years of initial tamoxifen therapy, extended adjuvant therapy with letrozole improved disease-free survival[10] and was superior to tamoxifen as neoadjuvant therapy.[11]

Recent reports of large trials indicate a better outcome among women given aromatase inhibitors than among those given tamoxifen in the adjuvant setting.[12,13] The Breast International Group (BIG) 1-98 study compared not only letrozole monotherapy with tamoxifen monotherapy as initial adjuvant endocrine therapy but also sequential treatment with the two agents in either order in postmenopausal women with hormone-receptor–positive breast cancer.

Methods

Study Design

BIG 1-98 is a randomized, phase 3, double-blind trial involving postmenopausal women with operable invasive breast cancer that was positive for estrogen receptors, progesterone receptors, or both. The women were randomly assigned to receive monotherapy with letrozole or tamoxifen for five years, letrozole for two years followed by tamoxifen for three years, or tamoxifen for two years followed by letrozole for three years. From March 1998 to March 2000, 1835 women were randomly assigned to monotherapy with either letrozole (2.5 mg daily) or tamoxifen (20 mg daily). From April 1999 to May 2003, an additional 6193 women were randomly assigned to one of the four groups (the CONSORT flow chart of the BIG 1-98 trial is shown in Fig. 1 in Supplementary Appendix 2, available with the full text of this article at www.nejm.org). Randomization was performed with the use of permuted blocks and was stratified according to the participating center and according to whether chemotherapy was neither given nor planned, was completed before randomization, or was planned to be given concurrently with endocrine therapy.

This protocol-specified primary analysis compares the two groups assigned to receive letrozole initially with the two groups assigned to receive tamoxifen initially. For this analysis, we included events and follow-up in the sequential-treatment groups that occurred up to 30 days after treatments were switched with events and follow-up in the monotherapy groups to increase the statistical power of the comparison of letrozole with tamoxifen. We also performed supplementary analyses comparing the monotherapy groups alone. The primary end point was disease-free survival, defined as the time from randomization to the first of one of the following events ending disease-free survival: recurrence at local, regional, or distant sites; a new invasive cancer in the contralateral breast; any second, nonbreast cancer; or death without a prior cancer event. Protocol-specified secondary end points included overall survival, defined as the time from randomization to death from any cause;

survival free of systemic disease (systemic disease–free survival), defined as the time from randomization to systemic recurrence (excluding local and contralateral-breast events), the occurrence of a second, nonbreast cancer, or death from any cause; and safety. Three additional end points that were not specified in the BIG 1-98 protocol were defined in the statistical-analysis plan because they were used as end points in other recently reported studies of aromatase inhibitors: disease-free survival as defined above, but excluding second, nonbreast cancers; the time to recurrence, defined as disease-free survival, but excluding second, nonbreast cancers and censoring data on patients who died without a recurrence of breast cancer; and the time to distant recurrence, defined as the time from randomization to the first recurrence at a distant site.

The study was coordinated by the International Breast Cancer Study Group (IBCSG), which was responsible for the study design, data collection and management, medical review, data analysis, and reporting (including the decision to publish). The ethics committees and required health authorities of each participating center approved the study protocol, and all patients gave written informed consent. In addition to the two planned interim analyses after the occurrence of 261 and 433 disease-free–survival events and the final efficacy analysis after 779 events, the IBCSG Data and Safety Monitoring Committee reviewed safety semiannually throughout the trial. Novartis, the manufacturer of letrozole (Femara), distributed the study drugs, provided financial support, and imposed no restrictions on the investigators with respect to trial data. The IBCSG Statistical Center had unblinded access to the database, and the IBCSG Data Management center had blinded access to the database. After the release of the results by the Data and Safety Monitoring Committee, the unblinded database was transferred to Novartis for the preparation of the clinical study report for health authorities. The manuscript was prepared by the Writing Committee, whose members made final decisions about content, and the Steering Committee (including employees of Novartis) reviewed the article and suggested changes. The Steering Committee chair (Dr. Thürlimann) vouches for the accuracy and completeness of the data.

STUDY POPULATION

Patients were eligible for the study if they were postmenopausal and had tumors that were positive for estrogen receptors, progesterone receptors, or both (definitions are provided in Fig. 1 of Supplementary Appendix 2). Primary surgery with resulting clear margins and adequate hematologic, renal, and hepatic function were required. Exclusion criteria included evidence of metastatic disease; previous or concurrent cancer other than adequately treated noninvasive breast or cervical cancer or basal-cell or squamous-cell carcinoma of the skin within 5 years before randomization; receipt of adjuvant antiestrogen therapy for the primary breast cancer for at least 1 month; and treatment with systemic investigational drugs within 30 days before randomization or topical investigational drugs within 7 days before randomization. The use of topical estrogens was discouraged during the trial. Before randomization, 2.1 percent had received neoadjuvant chemotherapy, 0.4 percent had received endocrine therapy for no longer than four months, and 39.3 percent had received hormone-replacement therapy more than four weeks before randomization (19.0 percent had done so within three months before randomization).

STUDY PROCEDURES

History taking and physical examination were performed at baseline, semiannually for the first five years, and yearly thereafter. Total cholesterol (90.8 percent of the values were not obtained after an overnight fast) was measured at baseline, semiannually for the first three years, yearly for the following two years, and one year after treatment ended. Hematologic and blood chemical measurements and bilateral mammograms were obtained at baseline and when medically indicated. Specific adverse events, which were listed on the case-report forms and graded according to the Common Toxicity Criteria of the National Cancer Institute (version 2) at each study visit during treatment, included myocardial infarction, cerebrovascular accident or transient ischemic attack, angina requiring percutaneous transluminal coronary angioplasty, angina requiring coronary-artery bypass grafting, a thromboembolic event, other cardiovascular events, hypercholesterolemia, bone fracture, vaginal bleeding, nausea, vomiting, hot flashes, and night sweats. Other adverse events

Table 1. Baseline Characteristics of the Patients, Tumors, and Primary Treatments.*

Characteristic	Letrozole (N=4003)	Tamoxifen (N=4007)	Overall (N=8010)
Menopausal category — no. (%)			
Postmenopausal before chemotherapy, if received	3857 (96.4)	3835 (95.7)	7692 (96.0)
Postmenopausal only after chemotherapy	92 (2.3)	100 (2.5)	192 (2.4)
Premenopausal (ineligible)	9 (0.2)	14 (0.3)	23 (0.3)
Uncertain postmenopausal status	44 (1.1)	58 (1.4)	102 (1.3)
Unknown or missing	1 (<0.1)	0	1 (<0.1)
Age at randomization — yr			
Median	61	61	61
Range	38–89	39–90	38–90
Tumor size — no. (%)			
≤2 cm	2496 (62.4)	2461 (61.4)	4957 (61.9)
>2 cm	1462 (36.5)	1511 (37.7)	2973 (37.1)
Unknown or missing	45 (1.1)	35 (0.9)	80 (1.0)
Nodal status — no. (%)			
Negative (including Nx)	2292 (57.3)	2295 (57.3)	4587 (57.3)
Positive	1660 (41.5)	1651 (41.2)	3311 (41.3)
Unknown or missing	51 (1.3)	61 (1.5)	112 (1.4)
ER and PgR status — no. (%)			
ER- and PgR-positive	2542 (63.5)	2513 (62.7)	5055 (63.1)
ER-positive and PgR-negative	808 (20.2)	823 (20.5)	1631 (20.4)
ER-positive and PgR status unknown or missing	579 (14.5)	575 (14.3)	1154 (14.4)
ER-negative and PgR-positive	60 (1.5)	83 (2.1)	143 (1.8)
ER status unknown or missing and PgR-positive	3 (0.1)	4 (0.1)	7 (0.1)
Other	11 (0.3)	9 (0.2)	20 (0.2)
Local therapy — no. (%)			
Breast-conserving surgery and radiotherapy	2134 (53.3)	2163 (54.0)	4297 (53.6)
Breast-conserving surgery and no radiotherapy	113 (2.8)	131 (3.3)	244 (3.0)
Mastectomy and radiotherapy	733 (18.3)	707 (17.6)	1440 (18.0)
Mastectomy and no radiotherapy	1016 (25.4)	995 (24.8)	2011 (25.1)
Other	7 (0.2)	11 (0.3)	18 (0.2)
Adjuvant or neoadjuvant chemotherapy (or both) received — no. (%)			
Yes†	1012 (25.3)	1012 (25.3)	2024 (25.3)
No	2991 (74.7)	2995 (74.7)	5986 (74.7)

* The patients included here make up the intention-to-treat group. Nx denotes 0 positive axillary lymph nodes with 1 to 7 nodes examined, ER estrogen receptor, and PgR progesterone receptor.

† A total of 1858 patients received adjuvant chemotherapy, 77 received neoadjuvant chemotherapy, and 89 received both adjuvant and neoadjuvant chemotherapy. A total of 642 patients received chemotherapy regimens that did not contain either an anthracycline or a taxane (621 of these patients received cyclophosphamide, methotrexate, and fluorouracil); 1301 received an anthracycline-containing regimen without a taxane; 78 received an anthracycline-containing regimen with a taxane and 3 received a taxane without anthracycline.

were also recorded but were not specifically listed on the case-report forms. Serious adverse events were reported in an expedited fashion.

Efficacy analyses were conducted on the basis of data received as of November 12, 2004. In March and April 2005, two senior oncologists at the IBCSG Coordinating Center conducted a medical review of all cardiovascular events of grade 3,

4, or 5 and other adverse events of grade 3, 4, or 5 that were considered clinically relevant but whose cause was unclear (affecting 538 patients), and all deaths of women who had had no prior cancer-related event (93 patients). Changes resulting from the medical review, all of which were agreed to by the investigators as required by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use under its Good Clinical Practice guidelines, were included in the safety analysis.

STATISTICAL ANALYSIS

The primary core analysis comparing letrozole with tamoxifen was designed to detect a 20 percent reduction in the risk of a disease-free–survival event (hazard ratio, 0.80) with a statistical power of 80 percent and a two-sided alpha level of 0.05. This design required a total of 647 events, allowing for two interim efficacy analyses based on the O'Brien–Fleming boundary.[14] Log-rank tests stratified according to randomization option and chemotherapy use (based on the randomized chemotherapy stratum) were used to compare the two groups,[15] and Kaplan–Meier estimates were calculated.[16] Cox proportional-hazards regression (with adjustment for randomization option and chemotherapy use) was used to adjust for various prognostic factors.[17] We used cumulative-incidence estimates and Gray's test[18] to control for competing risks and Fisher's exact tests to compare the percentages of patients with adverse events.[19]

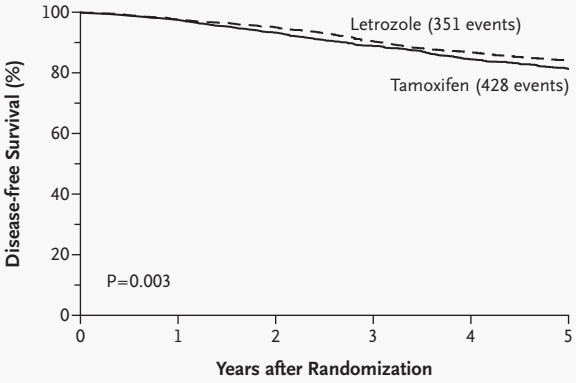
RESULTS

STUDY POPULATION

Among the 8028 enrolled patients, 18 withdrew consent and did not start treatment, leaving 8010 patients (4003 in the letrozole group and 4007 in the tamoxifen group) for analysis (see Fig. 1 in Supplementary Appendix 2). After randomization, 133 patients (1.7 percent) were deemed ineligible on the basis of a medical review (41 were not postmenopausal, 30 had a prior or concurrent cancer or bilateral breast cancer, 27 had cancer that was incorrectly staged, 17 had a negative or unknown hormone-receptor status, and 18 were ineligible for other reasons) but were included in this intention-to-treat analysis. Forty-seven patients (0.6 percent) did not receive any treatment and were excluded from all safety analyses, and 1717 patients who underwent hysterectomy before study entry were excluded from safety analyses of endometrial events. An additional 34 patients (0.4 percent) inadvertently received the opposite treatment for a median of 4.7 months but were evaluated according to their randomized assignment. The median follow-up for the primary core analysis was 25.8 months. Among patients who were alive and free of recurrence, 98.1 percent had a follow-up report within one year before the data cutoff. The baseline characteristics of the patients, tumors, and primary treatments were similar in the two groups (Table 1).

EFFICACY

Disease-free survival was significantly greater in the letrozole group than in the tamoxifen group (hazard ratio for the primary end point, 0.81; 95 percent confidence interval, 0.70 to 0.93; P=0.003 by the log-rank test) (Fig. 1), especially reducing recurrence at distant sites (hazard ratio, 0.73; 95 percent confidence interval, 0.60 to 0.88; P=0.001 by the log-rank test). The five-year estimates of disease-free survival were 84.0 percent in the letrozole group and 81.4 percent in the tamoxifen group (Fig. 1). Efficacy end-point events are shown in Table 2. A beneficial effect of letrozole was



Letrozole						
No. at risk	4003	3892	2964	1261	892	567
Disease-free survival (%)		97.7	95.1	90.5	86.8	84.0
Tamoxifen						
No. at risk	4007	3896	2926	1238	866	544
Disease-free survival (%)		97.6	93.4	89.0	84.6	81.4

Figure 1. Kaplan–Meier Estimates of Disease-free Survival.

The median follow-up was 25.8 months, and 1111 patients were free of disease for at least 5 years. The hazard ratio for the primary end point of recurrence at local, regional, or distant sites, a new invasive cancer in the contralateral breast, any second, nonbreast cancer, or death without a prior cancer event was 0.81 for the letrozole group, as compared with the tamoxifen group (95 percent confidence interval, 0.70 to 0.93; P=0.003 by the log-rank test).

Table 2. Incidence of Efficacy End-Point Events.

Event	Letrozole (N=4003)	Tamoxifen (N=4007)
	number (percent)	
Primary end point		
Disease-free–survival event*	351 (8.8)	428 (10.7)
Local recurrence	21 (0.5)	37 (0.9)
Contralateral-breast cancer	16 (0.4)	27 (0.7)
Regional recurrence	13 (0.3)	12 (0.3)
Distant recurrence	177 (4.4)	232 (5.8)
Soft tissue	11 (0.3)	19 (0.5)
Bone	80 (2.0)	99 (2.5)
Viscera	86 (2.1)	114 (2.8)
Second, nonbreast cancer	69 (1.7)	82 (2.0)
Death without prior cancer event	55 (1.4)	38 (0.9)
Secondary end points		
Death from any cause	166 (4.1)	192 (4.8)
Systemic disease-free–survival events (excluding local and contralateral-breast events)	323 (8.1)	383 (9.6)

* A disease-free–survival event was defined as the first of any of the following events: any breast-cancer recurrence; a new, invasive cancer in the contralateral breast; a second, nonbreast cancer; or death without a prior cancer event.

also seen in analyses comparing the two monotherapy groups (data not shown).

Letrozole significantly reduced the cumulative incidence of breast-cancer relapse as compared with tamoxifen. This difference became evident one year after randomization, and there was an absolute difference of 3.4 percentage points at five years (Fig. 2A). The cumulative incidence of second, nonbreast cancers did not differ significantly between the letrozole and tamoxifen groups (Fig. 2B). The cumulative incidence of death among women without a prior cancer event was higher in the letrozole group than in the tamoxifen group, but not significantly so (Fig. 2C).

Prospectively planned subgroup analyses of disease-free survival showed a greater effect of letrozole than of tamoxifen among patients who received chemotherapy, those who did not receive radiotherapy, and those with involved axillary lymph nodes (Fig. 3). For example, the five-year disease-free survival rate among patients with node-positive cancer was 77.9 percent in the letrozole group and 71.4 percent in the tamoxifen group; the value among patients with node-negative cancer was 88.7 percent in both groups. The beneficial effect of letrozole on disease-free survival was similar for all combinations of estrogen-receptor and progesterone-receptor status (Fig. 3).

Analysis of the secondary protocol-defined end points of overall survival and systemic disease–free survival also favored letrozole. Fewer women died in the letrozole group than in the tamoxifen group (166 patients [4.1 percent], as compared with 192 patients [4.8 percent]), but the overall survival did not differ significantly between groups. Figure 3 shows the hazard ratios for the three additional end points (disease-free survival, excluding second, nonbreast cancers; time to recurrence; and time to distant recurrence) in the letrozole group as compared with the tamoxifen group.

SAFETY

More patients in the letrozole group than in the tamoxifen group reported at least one protocol-specified adverse event of any grade (2912 patients vs. 2554 patients), but the number of patients with life-threatening or fatal protocol-specified adverse events was similar in the two groups (67 of 3975 [1.7 percent] and 69 of 3988 [1.7 percent], respectively). Fractures were significantly more frequent in the letrozole group than in the tamoxifen group (5.7 percent vs. 4.0 percent, P<0.001) (Table 3), with a significantly shorter time to a first fracture reported within four weeks after the end of treatment (P<0.001). As compared with tamoxifen, letrozole was associated with fewer thromboembolic events (1.5 percent vs. 3.5 percent, P<0.001), a lower rate of vaginal bleeding (3.3 percent vs. 6.6 percent, P<0.001), fewer endometrial biopsies (72 of 3089 women [2.3 percent] vs. 288 of 3157 women [9.1 percent], P<0.001), and fewer invasive endometrial cancers (4 of 3089 women [0.1 percent] vs. 10 of 3157 women [0.3 percent], P=0.18).

The respective median changes in cholesterol values from baseline to 6, 12, and 24 months were 0, 0, and –1.8 percent in the letrozole group and –12.0, –13.5, and –14.1 percent in the tamoxifen group. A total of 43.6 percent of patients in the letrozole group and 19.2 percent of patients in the tamoxifen group had hypercholesterolemia reported at least once during treatment (grade 1 in 35.1 percent and 17.3 percent, respectively). The overall incidence of adverse cardiovascular events of grade 3, 4, or 5 was similar in the two groups (3.7 percent in the letrozole group and 4.2 percent in the tamoxifen group), but more women in the letrozole group had grade 3, 4, or 5 cardiac events (2.1 percent vs. 1.1 percent, P<0.001) (Table 3).

DISCUSSION

Our study confirms the positive results reported in other trials of letrozole as adjuvant treatment for hormone-receptor–positive breast cancer in postmenopausal women[8-11] and provides new information concerning the use of an aromatase inhibitor in this setting.[12,13,20,21] Particularly notable was our finding of a significant reduction in the risk of distant recurrence with letrozole, as compared with tamoxifen (hazard ratio, 0.73; 95 percent confidence interval, 0.60 to 0.88; P=0.001). Longer follow-up is required to determine whether letrozole will continue to reduce the risk of relapse for several years after the cessation of treatment, as has been shown for tamoxifen.[22]

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial,[12,20,21] comparing anastrozole with tamoxifen, and our trial found similar hazard ratios for similarly defined end points (occurrences of ductal carcinoma in situ, but not second, nonbreast cancers, were counted as disease-free–survival events in the ATAC trial). In subgroup analyses of the ATAC trial, the benefit of anastrozole was seen predominantly in patients who had not received adjuvant chemotherapy and those with node-negative disease, whereas in the BIG 1-98 trial, the greatest benefit of letrozole was in patients who had received chemotherapy and in those with node-positive disease. We also found that all patients with estrogen-receptor–positive tumors had a similar reduction in the risk of a disease-free–survival event associated with letrozole irrespective of their progesterone-receptor status, whereas the ATAC trial showed a beneficial effect of anastrozole mainly in patients with estrogen-receptor–positive and progesterone-receptor–negative tumors.[23] These findings highlight the need for caution in interpreting subgroup analyses, even in large trials.

Our initial results suggest that an aromatase inhibitor should be considered in the adjuvant-treatment plan for postmenopausal women with hormone-sensitive breast cancer. The results of the BIG 1-98 trial show that tamoxifen and letrozole have different safety profiles. In patients at low risk for breast-cancer recurrence, the incidence, severity, type, and duration of side effects are relevant in selecting treatment.[24,25] The safety profile of letrozole in our study is in line with findings in earlier studies.

The increased incidence of fractures among women taking letrozole in our study suggests a

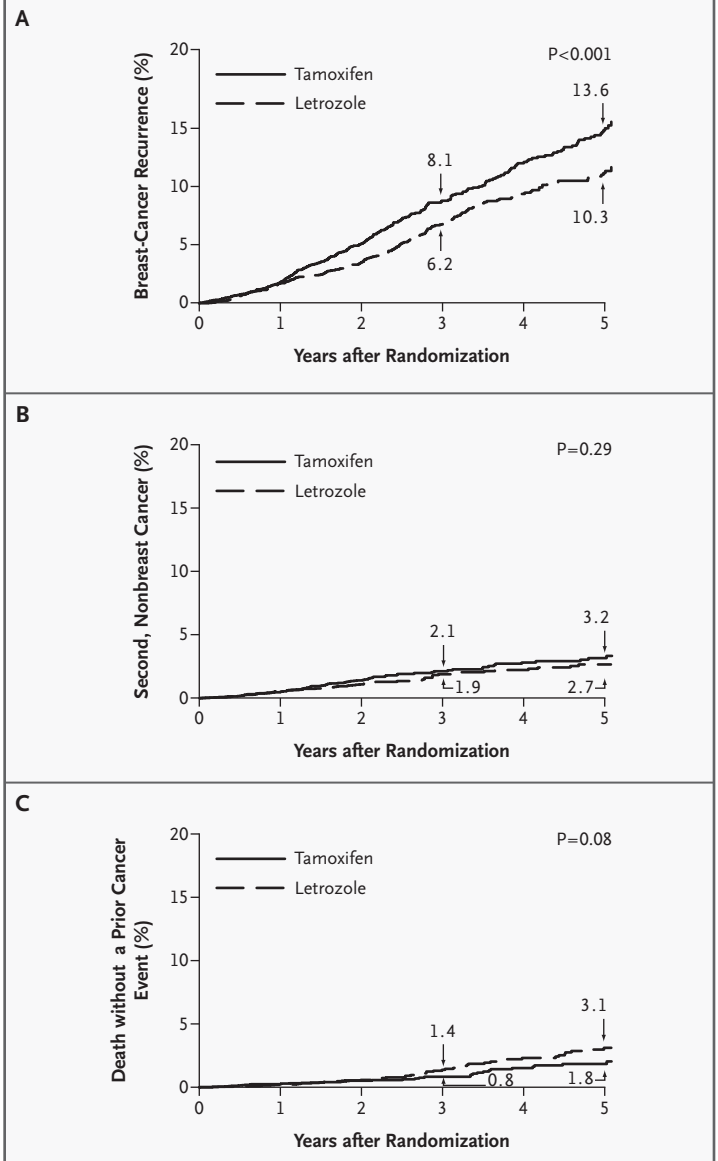


Figure 2. Cumulative Incidence of a Breast-Cancer Relapse (Panel A); a Second, Nonbreast Cancer (Panel B); and Death without a Prior Cancer Event (Panel C).

The second nonbreast cancers included endometrial cancer (6 patients in the letrozole group and 15 patients in the tamoxifen group), colon cancer (8 and 13 patients, respectively), lung cancer (5 and 8 patients), ovarian cancer (4 and 8 patients), renal cancer (4 and 8 patients), and other types (42 and 30 patients). Causes of death without a prior cancer event included cerebrovascular accident (7 patients in the letrozole group and 1 patient in the tamoxifen group), thromboembolic event (2 patients in each group), cardiac causes (13 and 6 patients, respectively), sudden death of unknown cause (10 patients in each group), and other causes (23 and 19 patients, respectively). Patients with multiple causes of death were classified as having "other causes." Two-sided P values for the cumulative incidence were calculated with the use of Gray's test.[18]

Variable	No. of Patients	No. of Events: Letrozole	No. of Events: Tamoxifen	Hazard Ratio (95% CI)	P Value
Primary end point					
Disease-free survival	8010	351	428	0.81 (0.70–0.93)	0.003
Age					
<65 yr	5143	187	230	0.82 (0.67–0.99)	0.04
≥65 yr	2867	164	198	0.79 (0.64–0.97)	0.02
Tumor size					
≤2 cm	4957	157	173	0.89 (0.72–1.10)	0.28
>2 cm	2973	190	251	0.76 (0.63–0.92)	0.004
Nodal status					
Negative (including Nx)	4587	140	147	0.96 (0.76–1.21)	0.75
Positive	3311	205	274	0.71 (0.59–0.85)	<0.001
ER and PgR status					
ER- and PgR-positive	5055	179	208	0.84 (0.69–1.03)	0.09
ER-positive and PgR-negative	1631	89	107	0.83 (0.62–1.10)	0.18
ER-positive and PgR status missing or unknown	1154	70	92	0.72 (0.53–0.98)	0.04
Local therapy					
Breast-conserving surgery	4548	128	155	0.86 (0.68–1.08)	0.20
Mastectomy	3452	223	271	0.76 (0.64–0.91)	0.003
Radiotherapy					
Yes	5744	227	273	0.82 (0.69–0.98)	0.03
No	2258	124	155	0.77 (0.61–0.98)	0.03
Chemotherapy					
Yes	2024	92	126	0.70 (0.54–0.92)	0.01
No	5986	259	302	0.85 (0.72–1.00)	0.06
Secondary end points					
Overall survival	8010	166	192	0.86 (0.70–1.06)	0.16
Systemic disease–free survival	8010	323	383	0.83 (0.72–0.97)	0.02
Additional end points					
Disease-free survival excluding 2nd nonbreast cancers	8010	296	369	0.79 (0.68–0.92)	0.002
Time to recurrence	8010	228	310	0.72 (0.61–0.86)	<0.001
Time to distant recurrence	8010	184	249	0.73 (0.60–0.88)	0.001

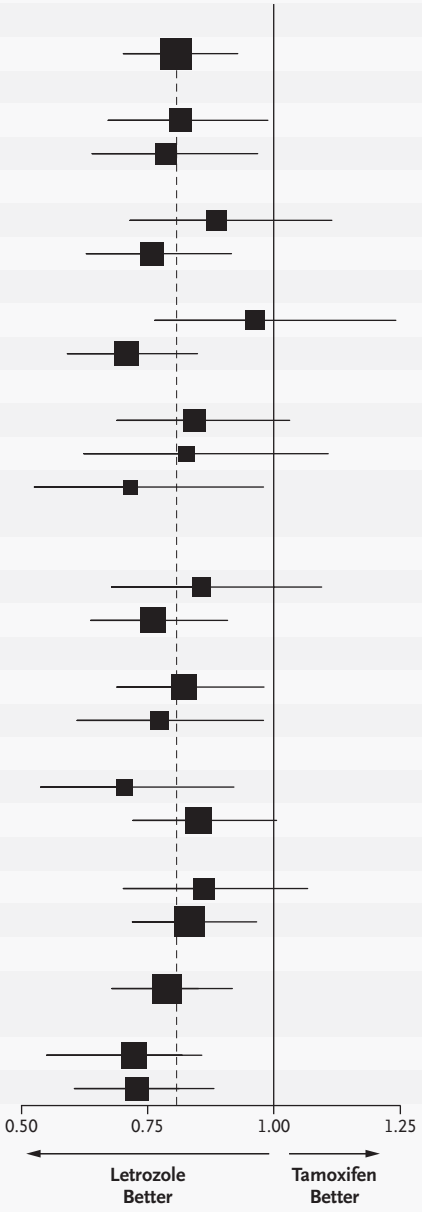


Figure 3. Cox Proportional-Hazards Model Results of Primary, Secondary, and Additional End Points.

The results were adjusted for randomization option and chemotherapy stratum. The size of the boxes is inversely proportional to the standard error of the hazard ratio. The dashed vertical line is placed at 0.81, the hazard-ratio estimate for the overall analysis of the primary study end point. Patients with missing data or unknown status were not included in the subgroup analyses. CI denotes confidence interval, ER estrogen receptor, and PgR progesterone receptor.

need for new approaches to reduce this risk, which is associated with estrogen deprivation. The absence of an increase in the median percent change from baseline in cholesterol levels during treatment with letrozole is similar to data from the MA.17 trial of the National Cancer Institute of Canada Clinical Trials Group, which compared letrozole with a placebo.[26] The low-grade hypercholesterolemia we found in patients given letrozole, but not tamoxifen, was also reported in a

Table 3. Incidence of Worst Grade of Adverse Events among Patients Included in the Safety Analysis.*

Adverse Event	Letrozole (N=3975)						Tamoxifen (N=3988)						P Value
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Any Grade	
	number of patients (percent)												
Cerebrovascular accident or TIA	ND†	ND†	20	15	4	39 (1.0)	1‡	ND†	22	17	1	41 (1.0)	0.91
Thromboembolic event	13†	17	22	7	2	61 (1.5)	17†	40	54	27	2	140 (3.5)	<0.001
Cardiac event	51	26	50	19	16	162 (4.1)	83	26	27	12	5	153 (3.8)	0.61
Ischemic heart disease	5	9	24	13	6	57 (1.4)	14	9	13	8	2	46 (1.2)	0.28
Cardiac failure	4	9	6	3	9	31 (0.8)	5	4	2	2	1	14 (0.4)	0.01
Other cardiovascular event	11	3	2	3	0	19 (0.5)	4	0	3	0	1	8 (0.2)	0.04
Vaginal bleeding	114	16	2	0	0	132 (3.3)	198	61	4	0	0	263 (6.6)	<0.001
Hot flashes	687	645	ND†	ND†	ND†	1332 (33.5)	704	812	ND†	ND†	ND†	1516 (38.0)	<0.001
Night sweats	295	259	ND†	ND†	ND†	554 (13.9)	313	334	ND†	ND†	ND†	647 (16.2)	0.004
Fracture	ND†	148	77	ND†	ND†	225 (5.7)	ND†	113	46	ND†	ND†	159 (4.0)	<0.001
Arthralgia	467	263	74	2	0	806 (20.3)	289	166	35	1	0	491 (12.3)	<0.001
Myalgia	156	72	25	1	0	254 (6.4)	176	50	16	1	0	243 (6.1)	0.61

* Adverse events were recorded during or within 28 days after study treatment. The adverse events reported in the table were recorded by the checking of specific boxes on the case-report forms, except in the case of arthralgia and myalgia, which were recorded in an "other" category and thus may have been underestimated. Grades were determined according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0), if available, and according to criteria defined by a senior IBCSG oncologist in the protocol otherwise. Fisher's exact P values are reported for the comparison of any grade and are not adjusted for multiple comparisons. TIA denotes transient ischemic attack.

† The grade was not defined (ND) according to the Common Toxicity Criteria of the National Cancer Institute (version 2.0); nevertheless, grade 1 thromboembolic events were reported and confirmed by investigators.

‡ This patient had a grade 1 cerebral microangiopathy.

small study[27] and may relate in part to the cholesterol-lowering effect of tamoxifen.[28,29]

The effect of estrogen deprivation and aromatase inhibitors on ischemic cardiac disease requires further study. The cause of the increased incidence of cardiac events of grade 3, 4, or 5 in the letrozole group, as compared with the tamoxifen group (2.1 percent vs. 1.1 percent), is unknown, but it may be due in part to a protective effect of tamoxifen on the arteries.[30,31] Some[32,33] but not all[34,35] groups have reported that tamoxifen has a cardioprotective effect. We agree with the technology-assessment statement issued by the American Society of Clinical Oncology in 2005 that current information is insufficient to determine fully the effect of aromatase inhibitors on cardiovascular disease, especially coronary heart disease.[24]

In conclusion, after a median follow-up of just over two years, our results indicate that letrozole is an effective option for standard adjuvant therapy, with a relatively favorable safety profile in postmenopausal women with endocrine-responsive breast cancer.

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Dr. Thürlimann reports having received consulting fees from AstraZeneca and Pfizer and owning stock in Novartis. Dr. Mouridsen reports having received consulting fees from Novartis, AstraZeneca, and Pfizer and lecture fees from Novartis; Dr. Mauriac, lecture fees from Novartis and, in his role with the French cancer group, a grant for central coordination for the BIG 1-98 trial; Dr. Forbes, consulting and lecture fees and grant support from various nonprofit agencies in his role as head of the Australian–New Zealand Breast Cancer Trials Group; Drs. Paridaens and Smith, research grants, lecture fees, and consulting fees from AstraZeneca, Novartis, and Pfizer; Dr. Wardley, consulting and lecture fees from Novartis; and Dr. Goldhirsch, consulting and lecture fees from GlaxoSmithKline, Novartis, AstraZeneca, Roche, and Schering-Plough. No other potential conflict of interest relevant to this article was reported.

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APPENDIX

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CORRECTION

A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer

A Comparison of Letrozole and Tamoxifen in Postmenopausal Women with Early Breast Cancer . On page 2747, in the list of members of the Writing Committee, the last name of Andrew Wardley was misspelled. We regret the error.

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