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Duration of Adjuvant Aromatase-Inhibitor Therapy in Postmenopausal Breast Cancer

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ABSTRACT

BACKGROUND

For postmenopausal women with hormone-receptor–positive breast cancer, the most effective duration for adjuvant therapy with an aromatase inhibitor remains unclear.

METHODS

In this prospective, phase 3 trial, we randomly assigned postmenopausal women with hormone-receptor–positive breast cancer who had received 5 years of adjuvant endocrine therapy to receive the aromatase inhibitor anastrozole for an additional 2 years (2-year group, receiving a total of 7 years) or an additional 5 years (5-year group, receiving a total of 10 years). The primary end point was disease-free survival. The primary analysis included all the patients who were still participating in the trial and who had no recurrence 2 years after randomization (i.e., when treatment in the 2-year group had ended). Secondary end points were overall survival, contralateral breast cancer, second primary cancer, and clinical bone fracture.

RESULTS

Among the 3484 women who were enrolled in the trial, 3208 remained in the trial without disease progression after the first 2 years of extended anastrozole treatment following randomization. Among these women, disease progression or death occurred in 335 women in each treatment group in the primary-analysis set at 8 years (hazard ratio, 0.99; 95% confidence interval [CI], 0.85 to 1.15; P=0.90). No between-group differences occurred in most secondary end points, and subgroup analyses did not indicate differences in any particular subgroup. The risk of clinical bone fracture was higher in the 5-year group than in the 2-year group (hazard ratio, 1.35; 95% CI, 1.00 to 1.84).

CONCLUSIONS

In postmenopausal women with hormone-receptor–positive breast cancer who had received 5 years of adjuvant endocrine therapy, extending hormone therapy by 5 years provided no benefit over a 2-year extension but was associated with a greater risk of bone fracture. (Funded by AstraZeneca and the Austrian Breast and Colorectal Cancer Study Group; ABCSG-16/SALSA ClinicalTrials.gov number, NCT00295620.)

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Luminal breast cancer is the most prevalent molecular subtype of this most frequent cancer in women,[1] with the majority of cases occurring after menopause. Despite substantial improvements in outcome resulting from the use of adjuvant endocrine therapy among women with luminal breast cancer,[2] the risk of disease recurrence continues indefinitely, with more than half the recurrences diagnosed after the first 5 years.[3] Thus, extending the duration of adjuvant endocrine therapy appears to be reasonable,[4] and large clinical trials have investigated this concept with both tamoxifen and aromatase inhibitors.[5]

In general, aromatase inhibitors are considered to be more effective than tamoxifen for the first 5 years of adjuvant therapy[6]; however, consecutive administration of tamoxifen and aromatase inhibitors represents an alternative.[7,8] After initial treatment with tamoxifen for 5 years, the addition of extended therapy has resulted in 40% longer disease-free survival than the use of placebo or no extended treatment.[9-11] In contrast, the benefit of extending aromatase-inhibitor therapy for 5 years beyond the original 5-year regimen is less well established.[12,13]

In addition, the most effective duration of such extension of therapy is unknown. However, the duration of therapy is an important variable because aromatase inhibitors have been associated with side effects that affect patients' quality of life. For example, sequelae such as hot flushes, arthralgia, and bone pain are frequently reported by patients taking these drugs, along with cognitive and behavioral side effects.[14] Consequently, treatment adherence has been compromised, and a substantial percentage of patients stop treatment prematurely, which has resulted in worse outcomes.[15] Treatment-induced osteoporosis, a consequence of aromatase-inhibitor therapy, has led to an increased incidence of bone fracture,[16,17] which has been associated with increased death, complications, and economic burden.[18]

In the Secondary Adjuvant Long-Term Study with Arimidex [anastrozole] (SALSA), we prospectively investigated whether an additional 2 years or 5 years of anastrozole therapy would result in better outcomes after the initial 5 years of endocrine therapy in postmenopausal women with hormone-receptor–positive breast cancer.

METHODS

TRIAL DESIGN AND OVERSIGHT

We conducted this investigator-initiated, multicenter, randomized, phase 3 trial in 75 centers in Austria. (The trial centers are listed in the Supplementary Appendix, available with the full text of this article and the protocol at NEJM.org.) An academic steering committee oversaw the trial design and conduct. The trial was performed in accordance with the Good Clinical Practice guidelines of the International Council for Harmonisation. The trial was approved by the institutional review board or ethics committee at each trial center. All the patients provided written informed consent.

Data and safety monitoring and collection and all data analyses were performed by the Austrian Breast and Colorectal Cancer Study Group (ABCSG) and the trial steering committee. The clinical database was hosted and maintained by ABCSG, and the trial sponsor, AstraZeneca, was the holder of the safety database and direct recipient of safety reports from the trial sites. The sponsor also partly funded the trial and provided the anastrozole used in the trial. The first author wrote the first draft of the manuscript, with input from the other authors. All the authors contributed to the interpretation of the data and to revisions in the manuscript and made the decision to submit the manuscript for publication. All the authors vouch for the integrity, accuracy, and completeness of the data and for the fidelity of the trial to the protocol and analysis plans.

PATIENTS AND RANDOMIZATION

We enrolled postmenopausal women who were 80 years of age or younger and who had histologically verified invasive hormone-receptor–positive breast cancer at an early stage (stage I, II, or III) without evidence of recurrence. All the women had received 5 years (±12 months) of adjuvant endocrine therapy with tamoxifen, aromatase inhibitors, or both sequentially up until 12 months before randomization. Additional details regarding inclusion and exclusion criteria are provided in Table S1 in the Supplementary Appendix.

We randomly assigned eligible patients in a 1:1 ratio to receive oral anastrozole (at a dose of

1 mg daily) as extended adjuvant endocrine treatment for either 2 additional years or 5 additional years. Randomization was performed by means of adaptive randomization using the minimization method,[19] according to the following stratification criteria: pathological tumor stage, pathological node stage, primary adjuvant endocrine therapy, adjuvant chemotherapy, receptor status, previous trial participation, and geographic region.

TRIAL PROCEDURES

Before randomization, to ensure disease-free status, we performed protocol-defined baseline investigations consisting of gynecologic examination, including vaginal ultrasonography; ultrasonography or computed tomography (CT) of the abdomen; chest radiography or CT; bilateral mammography; laboratory tests, including tumor markers CEA and CA 15-3; and measurement of bone density. Doses of anastrozole were not modified, but a temporary interruption (≤3 months) in treatment was permissible. Apart from anastrozole, no additional systemic breast cancer treatment was allowed. Bone-targeted interventions were recommended in case of treatment-induced osteoporosis, according to the relevant guidelines. During the treatment phase, clinical visits and radiologic examinations were scheduled to occur 6 months after the beginning of extended treatment and annually thereafter during the first 5 years. During follow-up after the treatment period, clinic visits were conducted and mammography was performed annually. The follow-up methods and scheduling of examinations were similar in the two trial groups.

Serious adverse events and adverse events leading to treatment discontinuation were recorded until 30 days after the last dose of the trial medication. No general recording of adverse events was performed during the trial, since the side-effect profile of anastrozole is well known and only different durations of therapy were being compared. Investigators monitored treatment adherence by giving patients bottles containing 112 tablets of anastrozole that were dated, labeled, and logged. Patients were requested to return the bottles with any remaining tablets at each visit.

END POINTS

The primary end point was disease-free survival among patients who were still participating in the trial at 2 years after randomization (i.e., when treatment in the 2-year group had ended) and who had no disease recurrence. Disease-free survival was defined as freedom from local or distant metastases, contralateral breast cancer, second primary cancer, or death without recurrence, evaluated in a time-to-event analysis. Secondary end points were the effect of the different treatment durations on overall survival and time-to-event analyses of the occurrence of contralateral breast cancer, second primary cancer, and first clinical fracture.

STATISTICAL ANALYSIS

Since the two groups of patients received the same therapy for the first 2 years of the trial, we did not expect to see a clinically significant difference between the groups until after endocrine treatment was stopped in the 2-year group. Therefore, we chose a time point 2 years after randomization as the starting point for the time-to-event analyses. We determined that enrollment of approximately 3500 patients would result in 433 patients who had disease recurrence or died within an observation period starting 2 years after randomization, with a target hazard ratio of 0.74 for the comparison between the 5-year group and the 2-year group; these calculations were based on anticipated disease-free survival rates of 94% and 92%, respectively, 5 years after randomization. We calculated that this number of events would provide 85% power to detect this difference at a two-sided significance level of 5% on the basis of a dropout rate of 5% during the first 2 years. A total trial period of 10 years (including the treatment phase and follow-up phase) was planned for each patient.

The primary analysis included all the patients who had remained in the trial and had no recurrence at 2 years. We performed Kaplan–Meier analyses and log-rank tests and used Cox proportional-hazards regression to estimate hazard ratios and corresponding 95% confidence intervals. The proportional-hazards assumption was tested by assessing the interaction between treatment assignment and the logarithm of the time variable in the Cox regression models. In order

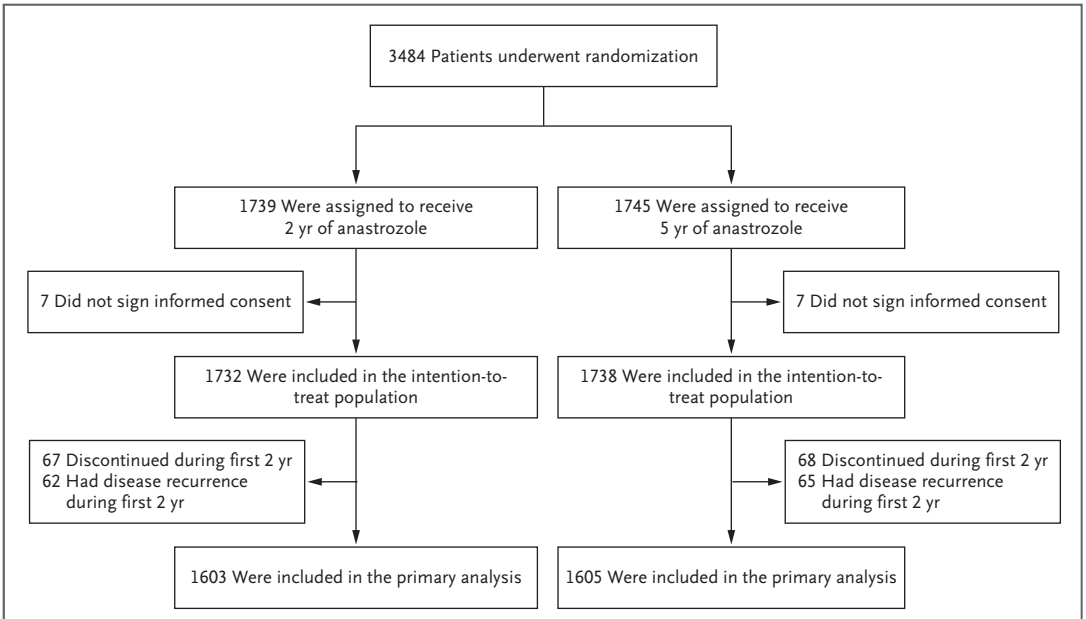

Figure 1. Enrollment and Outcomes.

Among the patients who had undergone randomization, the primary analysis of disease-free survival included all those who were still participating in the trial and had no recurrence event 2 years after randomization.

to adjust for potential confounding effects, we performed additional multivariate Cox analyses with consideration of the stratification criteria used for randomization (except region), as well as the patient's age at randomization, histologic tumor grade, and status with respect to previous radiotherapy.

Cox models were also used for the post hoc between-group comparison of outcomes within subgroups, which were categorized according to the patients' demographic, clinical, and tumor characteristics at baseline. An exploratory post hoc analysis of competing risks was based on distant recurrence as the event of interest and death as the competing event. Sensitivity analyses starting at the time of randomization were performed for outcomes except for the time-to-event analysis of clinical bone fracture (since the proportional-hazards assumption was not met). In addition, we performed a post hoc analysis of subgroups based on treatment adherence and post hoc landmark analyses of disease-free survival that involved between-group comparisons of all the patients in the two groups and of only those who were adherent to the trial regimen at years 2 through 5 in half-year intervals. In an additional post hoc analysis, we calculated the absolute risk reduction in the time until clinical bone fracture, along with the number of patients who would need to be treated for benefit or harm with respect to this secondary end point.[20] All analyses were performed with the use of SAS statistical software, versions 9.3 and 9.4 (SAS Institute).

RESULTS

PATIENTS AND FOLLOW-UP

From February 2004 through June 2010, a total of 3484 postmenopausal women with hormone-receptor–positive breast cancer at an early stage (i.e., I, II, or III) underwent randomization. After 14 patients did not provide signed informed consent, the full analysis set (intention-to-treat population) consisted of 3470 patients (1732 in the 2-year group and 1738 in the 5-year group) (Fig. 1). The two groups were well balanced with respect to clinical and demographic characteristics at baseline (Table S2). The median age at the time of randomization was 64 years, 2508 patients (72.3%) had tumors that were smaller than 2 cm, 2302 (66.3%) had node-negative dis-

ease, and 674 (19.4%) had high-grade tumors. Positivity for both estrogen and progesterone receptors was found in 2684 patients (77.3%), and 2765 (79.7%) had been treated with breast-conserving surgery. A total of 1000 patients (28.8%) had also received neoadjuvant chemotherapy, and 2780 (80.1%) had undergone adjuvant radiotherapy. In the primary-analysis population of 3208 patients, 1635 (51.0%) had received tamoxifen alone for the initial 5 years, 235 (7.3%) had received an aromatase inhibitor alone, and 1338 (41.7%) had received an aromatase inhibitor in combination with tamoxifen (Table 1).

EFFICACY

The median follow-up after randomization was 118.0 months (interquartile range, 97.8 to 121.1). Starting at 2 years after randomization (during which 262 patients dropped out of the analysis set), disease progression or death occurred in 670 of 3208 patients (20.9%), with 335 in each treatment group. Locoregional events occurred as first events in 87 patients (2.7%), and 68 patients (2.1%) had a contralateral breast cancer (Table 2). Distant recurrence occurred in 160 patients (5.0%), and secondary cancers occurred in 208 (6.5%) as first events; 151 patients (4.7%) died without previous recurrence.

With respect to the primary end point (disease-free survival starting 2 years after randomization), the results at 8 years after the end of treatment in the 2-year group (10 years since randomization) were similar in the two treatment groups (73.6% in the 2-year group and 73.9% in the 5-year group), with a hazard ratio for disease recurrence or death of 0.99 (95% confidence interval [CI], 0.85 to 1.15; P=0.90) (Fig. 2A). A similar result was obtained after adjustment for potential confounding factors (hazard ratio, 1.00; 95% CI, 0.86 to 1.16). No between-group difference was noted for overall survival at 8 years (87.5% in the 2-year group and 87.3% in the 5-year group), with a hazard ratio for death from any cause of 1.02 (95% CI, 0.83 to 1.25) (Fig. 2B). The hazard ratio for contralateral breast cancer was 1.15 (95% CI, 0.75 to 1.77) (Fig. S1A), and the hazard ratio for a second primary cancer was 1.06 (95% CI, 0.81 to 1.38) (Fig. S1B).

Subgroup analyses did not indicate that a particular subgroup benefited more than another in either treatment group (Figs. S2 and S3). In a competing-risk analysis of distant recurrence, with death as the competing event, the results were similar in the two groups (hazard ratio, 0.99; 95% CI, 0.74 to 1.31). However, there was a slightly lower risk for patients in the 5-year group after approximately 5 years of treatment with respect to the cumulative incidence curves (Fig. S4). Sensitivity analyses comparing the between-group differences from randomization showed similar findings in all cancer-related end points and in subgroup analyses (Figs. S5 through S8 and Table S3).

BONE FRACTURE

The risk of clinical bone fracture at 5 years after randomization was lower in the 2-year group than in the 5-year group (4.7% vs. 6.3%; hazard ratio, 1.35; 95% CI, 1.00 to 1.84) (Fig. 3A). This difference in fracture risk occurred despite the equivalent use of bone-targeted medications in the two groups (Table S4). From 3 to 5 years, the increased risk in the 5-year group was indicated by negative values of absolute risk reduction. At 5 years, the number of patients who would need to be treated to result in harm to a patient (number needed to harm) was 63 (95% CI, 32 to 953) (Fig. 3B).

ADVERSE EVENTS

Side effects of anastrozole were in line with the known toxicity profile of the drug. At least one serious adverse event occurred in 452 of 1705 patients (26.5%) in the 2-year group and in 687 of 1710 (40.2%) in the 5-year group; serious adverse events that were deemed by the investigator to be related to anastrozole occurred in 40 patients (2.3%) and 69 patients (4.0%), respectively. Osteoarthritis was the most frequently reported adverse event and was documented in 29 patients (1.7%) in the 2-year group and in 74 (4.3%) in the 5-year group. A full list of serious adverse events is provided in Table S5.

TREATMENT ADHERENCE

A similar percentage of patients in the two trial groups discontinued extended anastrozole therapy over time (Fig. S9). Within the first 2 years after randomization, approximately 20% of the patients were no longer taking anastrozole, a

Table 1. Characteristics of the Patients in the Primary-Analysis Population.*

Characteristic	Extended Anastrozole for 2 Years (N=1603)	Extended Anastrozole for 5 Years (N=1605)	All Patients (N=3208)
Age at randomization — yr			
Mean ±SD	64.1±7.9	63.9±7.7	64.0±7.81
Median (IQR)	64 (58–70)	64 (59–69)	64 (59–69)
Range	38–84	29–80	29–84
Tumor stage — no. (%)			
T1	1172 (73.1)	1163 (72.5)	2335 (72.8)
T2	397 (24.8)	405 (25.2)	802 (25.0)
T3	29 (1.8)	29 (1.8)	58 (1.8)
Tx	3 (0.2)	6 (0.4)	9 (0.3)
Unknown	2 (0.1)	2 (0.1)	4 (0.1)
Nodal stage — no. (%)			
N0	1065 (66.4)	1081 (67.4)	2146 (66.9)
N1	504 (31.4)	484 (30.2)	988 (30.8)
N2	27 (1.7)	33 (2.1)	60 (1.9)
N3	5 (0.3)	7 (0.4)	12 (0.4)
Unknown	2 (0.1)	0	2 (0.1)
Histologic grade — no. (%)			
G1	230 (14.3)	241 (15.0)	471 (14.7)
G2	1031 (64.3)	1021 (63.6)	2052 (64.0)
G3	296 (18.5)	313 (19.5)	609 (19.0)
Gx	24 (1.5)	10 (0.6)	34 (1.1)
Unknown	22 (1.4)	20 (1.2)	42 (1.3)
Hormone-receptor status — no. (%)			
Estrogen-receptor positive and progesterone-receptor positive	1262 (78.7)	1230 (76.6)	2492 (77.7)
Estrogen-receptor negative and progesterone-receptor negative	0	1 (0.1)	1 (<0.1)
Either estrogen-receptor negative or progesterone-receptor negative†	341 (21.3)	370 (23.1)	711 (22.2)
Unknown	0	4 (0.2)	4 (0.1)
Type of surgery — no. (%)			
Breast conservation	1271 (79.3)	1306 (81.4)	2577 (80.3)
Mastectomy	328 (20.5)	290 (18.1)	618 (19.3)
Other	4 (0.2)	9 (0.6)	13 (0.4)
Previous endocrine therapy — no. (%)			
Aromatase inhibitor	117 (7.3)	118 (7.4)	235 (7.3)
Tamoxifen	816 (50.9)	819 (51.0)	1635 (51.0)
Tamoxifen plus aromatase inhibitor	670 (41.8)	668 (41.6)	1338 (41.7)
Previous chemotherapy — no. (%)			
Containing anthracycline	230 (14.3)	218 (13.6)	448 (14.0)
Containing taxane	84 (5.2)	87 (5.4)	171 (5.3)

Table 1. (Continued.)

Characteristic	Extended Anastrozole for 2 Years (N=1603)	Extended Anastrozole for 5 Years (N=1605)	All Patients (N=3208)
Other chemotherapy	153 (9.5)	150 (9.3)	303 (9.4)
No chemotherapy	1136 (70.9)	1149 (71.6)	2285 (71.2)
Unknown	0	1 (0.1)	1 (<0.1)
Previous radiotherapy — no. (%)			
Yes	1279 (79.8)	1300 (81.0)	2579 (80.4)
No	324 (20.2)	305 (19.0)	629 (19.6)

* Included in the primary time-to-event analysis of disease-free survival were all the patients who were still participating in the trial and had no disease recurrence 2 years after randomization. IQR denotes interquartile range.
† A total of 630 patients (302 in the 2-year group and 328 in the 5-year group) had breast cancer that was estrogen-receptor positive and progesterone-receptor negative; 81 patients (39 in the 2-year group and 42 in the 5-year group) had disease that was estrogen-receptor negative and progesterone-receptor positive.

Table 2. Events Contributing to the Primary End Point.*

Event	Extended Anastrozole for 2 Years (N=1603)	Extended Anastrozole for 5 Years (N=1605)	All Patients (N=3208)
		number (percent)	
Local or distant recurrence, contralateral breast cancer, second primary cancer, or death without recurrence	335 (20.9)	335 (20.9)	670 (20.9)
Local recurrence	48 (3.0)	39 (2.4)	87 (2.7)
Distant recurrence	82 (5.1)	78 (4.9)	160 (5.0)
Contralateral breast cancer	35 (2.2)	33 (2.1)	68 (2.1)
Second primary cancer	100 (6.2)	108 (6.7)	208 (6.5)
Death without recurrence	70 (4.4)	81 (5.0)	151 (4.7)

* Shown are data for all the patients in the intention-to-treat group who were included in the primary analysis. A total of 3 patients had local and distant recurrences at the same time, and 1 patient had a local recurrence and a contralateral breast cancer at the same time.

percentage that increased to approximately 33% by 5 years. The results of exploratory survival analyses in the subgroup of patients who had medication adherence were similar to the findings in the intention-to-treat population. Similar results were seen in the two groups with respect to disease-free survival (hazard ratio for disease recurrence or death, 0.91; 95% CI, 0.76 to 1.09), overall survival (hazard ratio for death from any cause, 0.92; 95% CI, 0.72 to 1.16), contralateral breast cancer (hazard ratio, 0.98; 95% CI, 0.60 to 1.60), and a second primary cancer (hazard ratio, 1.20; 95% CI, 0.89 to 1.63). Landmark analyses of disease-free survival showed some slightly better outcomes in the subgroup of patients who adhered to their medication regimen (Table S6).

DISCUSSION

The specific goal of this trial was to assess the benefits and harms of extending aromatase-inhibitor therapy beyond a total treatment duration of 7 years in postmenopausal women, the population in which breast cancer is most frequently diagnosed. At a median follow-up of nearly 10 years (i.e., a median of 15 years after the first diagnosis of breast cancer), we found that a 5-year extension of adjuvant therapy with the aromatase-inhibitor anastrozole was not as-

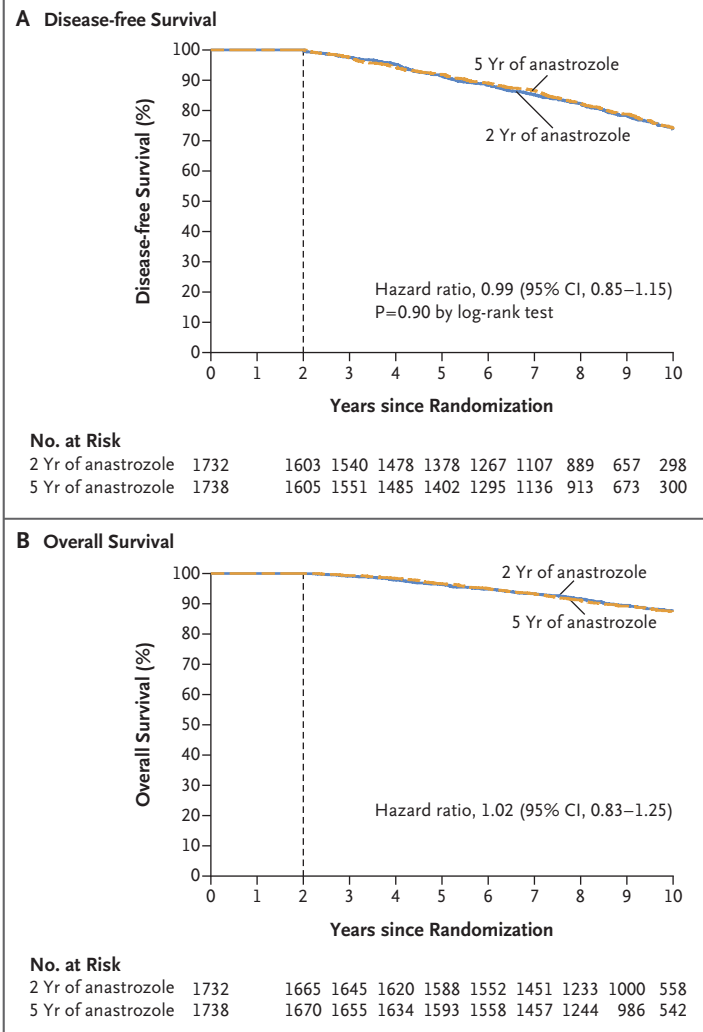

Figure 2. Kaplan–Meier Estimates of Survival.

The primary end point of disease-free survival (Panel A) and a secondary end point of overall survival (Panel B) are shown for postmenopausal women with hormone-receptor–positive breast cancer who received extended adjuvant anastrozole therapy for either 2 years or 5 years after 5 years of initial adjuvant endocrine therapy (tamoxifen, aromatase inhibitors, or both in sequence). The starting point for the analyses at 2 years after randomization (when treatment in the 2-year group had ended) is indicated by the vertical dashed line. At 8 years after the end of treatment in the 2-year group (10 years since randomization), disease-free survival was 73.6% in the 2-year group and 73.9% in the 5-year group; overall survival percentages were 87.5% and 87.3%, respectively.

sociated with a better outcome than a 2-year extension with respect to disease-free survival. Although disease-free survival and overall survival were similar in the two trial groups, the prolongation of anastrozole therapy led to additional side effects and resulted in more treatment-related clinical bone fractures.

In this trial, we did not investigate the value of extending adjuvant endocrine therapy per se, since the benefit of extending aromatase inhibitors after 5 years of adjuvant tamoxifen has been well established.[9-11] In contrast, the most effective duration of adjuvant aromatase-inhibitor therapy remains unclear in randomized trials. In two such trials, investigators assigned patients who had received 5 years of adjuvant aromatase-inhibitor therapy to receive an additional 5 years of letrozole or placebo. In the MA.17R trial, patients who received extended letrozole therapy had significantly longer disease-free survival than those who received placebo (hazard ratio for disease recurrence or death, 0.66; 95% CI, 0.48 to 0.91; P=0.01). However, this better outcome was driven mainly by a decrease in second primary breast cancers, and no significant benefit was observed in any of the predefined subgroups.[13] In the primary analysis of the National Surgical Adjuvant Breast and Bowel Project 42 (NSABP-42) trial, investigators did not find a disease-free survival benefit among patients who received 5 years of extended aromatase-inhibitor treatment after an initial 5 years of aromatase inhibitors or sequential treatment with tamoxifen and an aromatase inhibitor.[12]

In two other randomized trials, investigators assigned postmenopausal women with breast cancer to receive different durations of aromatase-inhibitor therapy. In the Extended Adjuvant Aromatase Inhibition after Sequential Endocrine Therapy (DATA) trial, which compared 3 years of anastrozole therapy with 6 years of therapy after 2 to 3 years of adjuvant tamoxifen, a longer therapy duration was not superior to a shorter duration.[21] In the Investigation on the Duration of Extended Letrozole (IDEAL) trial, in which patients were randomly assigned to receive either 2.5 years or 5 years of letrozole after an initial 5 years of endocrine therapy, no difference in disease-free survival was observed.[22] Thus, no overall survival benefit was seen for a longer treatment duration in either of these trials.

Taking these results together, we concluded that there was no firm evidence of a benefit for prolonged aromatase-inhibitor therapy in postmenopausal patients with hormone-receptor–positive breast cancer who are at average risk for

recurrence. In line with some positive signals from retrospective subgroup analyses in other trials or meta-analyses, we also observed minor, nonsignificant temporary benefits in exploratory post hoc analyses. In view of the persistent risk of recurrence in luminal breast cancer, the concept of treatment prolongation remains compelling, but most results that support this risk-stratified recommendation are derived from retrospective studies or subgroup analyses.[23,24]

The effect of extended aromatase-inhibitor treatment on patients' quality of life is not trivial, since musculoskeletal symptoms such as arthralgia and bone and joint pain frequently occur, and these sequelae may persist for years.[25] Almost half of all patients in some studies have cognitive impairments, sexual dysfunction, mood changes, or weight gain.[26,27] Although, as expected, the prevalence of these side effects was similar in the two groups in our trial, it is evident that having these sequelae and being at risk for them for 3 additional years was a disadvantage for patients in the 5-year group. Even though these side effects can be alleviated by pharmaceutical and lifestyle interventions,[28,29] their occurrence often leads to a high rate of nonadherence to treatment.[30] The observed adherence to the assigned regimens was somewhat higher in our trial than adherence reported in other trials, but we still observed a consistent drop-off of patients, a factor that would probably be markedly higher outside a clinical trial.[15,31] Even when analyses were confined to treatment-adherent patients, no relevant change in results was seen, and a longer treatment extension did not yield benefit. In addition, investigators have found that acquired resistance may occur in dormant tumor cells during prolonged therapeutic pressure.[32]

The clinically relevant toxicity of aromatase inhibitors is the deleterious effect of estrogen depletion on bone health.[33] Not surprisingly, we observed an excess of fractures in the 5-year group. Although the personal risk of fracture varies according to age, body-mass index, and other individual factors,[34] the consequences of bone fracture on morbidity and quality of life as well as health care costs may outweigh the benefits of adjuvant endocrine therapy.[20] Data have indicated that fracture incidence is most likely underreported in breast cancer trials that focus on disease recurrence.[33] Antiresorptive agents can counteract the effects of aromatase inhibitors,[35,36] but their use is counterbalanced by additional toxic effects and expense.[37] The exploratory number-needed-to-harm analysis of this trial confirmed that prolongation of extended aromatase-inhibitor treatment beyond 7 years

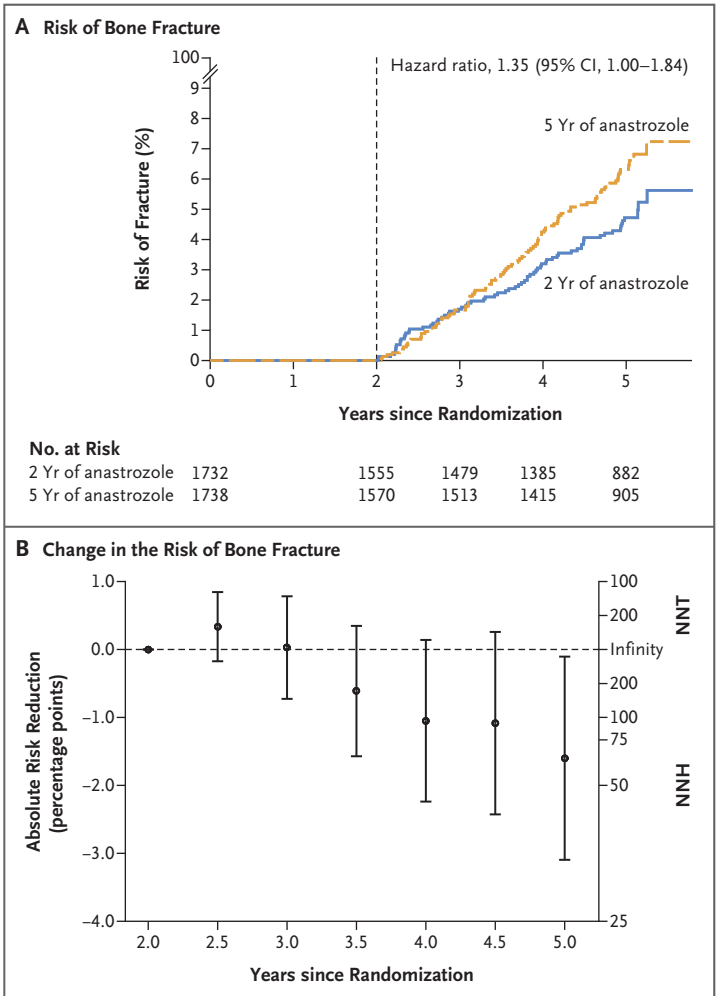

Figure 3. Clinical Bone Fracture and Absolute Risk Reduction.

Panel A shows Kaplan–Meier estimates of the time until the first clinical bone fracture in the 2-year group and the 5-year group. The vertical dashed line indicates the starting point for the analyses at 2 years after randomization, when treatment in the 2-year group had ended. Panel B shows the absolute change in the risk of fracture with prolonged endocrine therapy during a 5-year period as compared with a 2-year period, as measured in percentage points. An increase in the risk of fracture in the 5-year group is indicated by a negative value for the absolute risk reduction. Accordingly, the number needed to harm (NNH) decreases by the end of the 3-year period (i.e., the risk of harm is greater). The I bars represent 95% confidence intervals. NNT indicates the number needed to treat to provide benefit.

resulted in potential harm for patients without providing outcome benefits.

Limitations of our trial include the administration of only one aromatase inhibitor, anastrozole. However, no data have indicated differences in efficacy among the three current aromatase inhibitors.[38,39] Also, the risk profile of our trial population did not focus on the highest-risk patients but rather represents an average-risk group of postmenopausal women with breast cancer. Consequently, we cannot fully rule out a small benefit for the highest-risk patients. Among patients at highest risk, several attempts to identify those at increased risk on the basis of clinicopathological or molecular features have been described.[40,41]

Thus, in postmenopausal women with hormone-receptor–positive breast cancer who had received 5 years of adjuvant endocrine therapy, the extension of aromatase-inhibitor therapy for 2 years rather than 5 years was sufficient to maximize the benefits of such therapy in most patients without extending the exposure to toxic effects.

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Disclosure forms as provided by the authors are available at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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