ARTICLE

Extended Adjuvant Therapy With Anastrozole Among Postmenopausal Breast Cancer Patients: Results From the Randomized Austrian Breast and Colorectal Cancer Study Group Trial 6a

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On behalf of the Austrian Breast and Colorectal Cancer Study Group

Background Clinical trial data have shown that among breast cancer patients who were disease free after 5 years of adjuvant treatment with tamoxifen, further extended treatment with the nonsteroidal aromatase inhibitor letrozole reduces breast cancer recurrence. We examined the efficacy and tolerability of extended adjuvant therapy with another aromatase inhibitor, anastrozole, for 3 years among women who had completed 5 years of adjuvant therapy.

Methods Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 6a is an extension of ABCSG Trial 6, in which hormone receptor–positive postmenopausal patients received 5 years of adjuvant tamoxifen, with or without the aromatase inhibitor aminoglutethimide, for the first 2 years of therapy. For ABCSG Trial 6a, patients who were disease free at the end of Trial 6 were randomly assigned to receive either 3 years of anastrozole or no further treatment. Efficacy data were analyzed with the use of a Cox proportional hazards regression model with two-sided *P* values and Kaplan–Meier curves, and tolerability data were estimated using logistic regression analysis with odds ratios and 95% confidence intervals (CIs).

Results ABCSG Trial 6a included 856 patients. At a median follow-up of 62.3 months, women who received anastrozole (n = 387) had a statistically significantly reduced risk of recurrence (locoregional recurrence, contralateral breast cancer, or distant metastasis) compared with women who received no further treatment (n = 469; hazard ratio = 0.62; 95% CI = 0.40 to 0.96, *P* = .031). Anastrozole was well tolerated, and no unexpected adverse events were reported.

Conclusions These data confirm the benefit of extending adjuvant tamoxifen therapy beyond 5 years with anastrozole compared with no further treatment. Further research is required to define the optimum length of extended adjuvant therapy and to investigate the possibility of tailoring this period to suit different disease types.

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Five years of adjuvant tamoxifen has been the standard endocrine treatment for early-stage breast cancer for several decades. Adjuvant endocrine therapy following primary surgery for breast cancer reduces the risk of recurrence and increases overall survival beyond the period of treatment for women with estrogen receptor (ER)–positive disease (1). Mature meta-analysis data on 15-year recurrence and breast cancer mortality probabilities demonstrate substantial and persistent benefits of receiving adjuvant tamoxifen compared with no adjuvant treatment (1). Most of the effect of adjuvant tamoxifen on recurrence is seen during the first 5 years after surgery, when tamoxifen is generally still administered, with gains in recurrence-free survival of 11.4%. However, many women who are treated with 5 years of adjuvant tamoxifen still develop recurrent disease, and most of the effect of adjuvant tamoxifen on breast cancer mortality occurs after the fifth year after surgery.

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CONTEXT AND CAVEATS

Prior knowledge

A large clinical trial found that women who received 5 years of the nonsteroidal aromatase inhibitor letrozole after 5 years of adjuvant tamoxifen experienced a 42% reduction in the risk of recurrence compared with women who received placebo. However, early stoppage of that trial precluded assessments of the long-term efficacy and safety of extended adjuvant treatment.

Study design

Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 6a was a prospective randomized open-label clinical trial to compare the efficacy and tolerability of extended adjuvant therapy with anastrozole for 3 years with no further treatment among patients who were disease free at the end of ABCSG Trial 6, which found that adjuvant tamoxifen plus the aromatase inhibitor aminoglutethimide was not superior to adjuvant tamoxifen alone in hormone receptor–positive postmenopausal breast cancer patients.

Contribution

At a median follow-up of more than 5 years, extended adjuvant therapy with 3 years of anastrozole after successful completion of 5 years of tamoxifen reduced the risk of recurrence by 38% compared with no further treatment. Anastrozole was well tolerated, and no unexpected adverse events were reported.

Implications

The more manageable side effect profile of anastrozole compared with tamoxifen may allow the duration of adjuvant treatment to extend beyond the 5-year period recommended for tamoxifen.

Limitations

A prerandomization procedure was used to randomly assign all eligible patients in ABCSG Trial 6 (i.e., all those who remained in the trial and disease free) to an arm of Trial 6a to ensure that there would be no gap in treatment between completion of 5 years of primary adjuvant therapy and commencement of the extended study.

The absolute survival benefit for women with ER–positive disease who received 5 years of adjuvant tamoxifen compared with women who did not was almost three times greater at 15 years of follow-up (9.2%) than at 5 years of follow-up (3.6%) (1,2).

A 5-year period for adjuvant monotherapy in postmenopausal women was adopted because of the risk–benefit profile of tamoxifen, rather than because an optimum length for adjuvant endocrine therapy had been determined. Current data indicate that approximately 10 years of adjuvant tamoxifen treatment does not produce additional overall survival benefits compared with 5 years of treatment, partly because of the increased risk of thromboembolic disease (1). In addition, the risk of endometrial cancer associated with tamoxifen use increases with treatment duration (1,3,4). Other studies have also failed to demonstrate a reduced risk of recurrence with more than 5 years of adjuvant tamoxifen (3,5,6). Clinical trials such as the Adjuvant Tamoxifen Treatment—Offer More? and Adjuvant Tamoxifen Longer Against Shorter trials are in progress to more accurately define the advantages and disadvantages of different lengths of adjuvant tamoxifen therapy. However, in the meantime, the 5-year period of treatment has become standard for adjuvant therapy in postmenopausal women, regardless of the agent employed.

In recent years, aromatase inhibitors have become widely accepted as alternatives to tamoxifen as the standard adjuvant treatment for postmenopausal women with hormone-sensitive early-stage breast cancer. Five years of adjuvant treatment with the third-generation nonsteroidal aromatase inhibitor anastrozole is superior to tamoxifen treatment in postmenopausal women in terms of both efficacy and safety, as demonstrated by data from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial at a median follow-up of 68 months (7). There are also efficacy and safety benefits associated with switching to anastrozole in patients who are disease free after 2–3 years of adjuvant tamoxifen therapy (8–11).

Data from the National Cancer Institute of Canada MA.17 trial showed that breast cancer recurrence was statistically significantly ($P<.001$) reduced in patients who were disease free after 5 years of adjuvant treatment with tamoxifen by further treatment with letrozole, another third-generation nonsteroidal aromatase inhibitor (12). Although this was the first trial to demonstrate the benefit of extending the period of adjuvant letrozole treatment beyond 5 years, it was halted early at a median follow-up of 30 months. Thus, no long-term efficacy or safety data are available from this randomized clinical investigation.

We sought to investigate the efficacy of extended adjuvant therapy with anastrozole in breast cancer patients who remain recurrence free after 5 years of adjuvant tamoxifen. We conducted a randomized trial (Trial 6a) to compare extended adjuvant therapy with anastrozole for 3 years with no further treatment among women who had completed 5 years of adjuvant therapy in Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 6. We examined recurrence-free and overall survival as well as tolerability. ABCSG Trial 6 had found that adjuvant tamoxifen plus the aromatase inhibitor aminoglutethimide was not superior to adjuvant tamoxifen alone in postmenopausal women with primary, hormone receptor–positive breast cancer (13).

Patients and Methods

Patients

ABCSG Trial 6a was a prospective randomized open-label clinical study that was a continuation of ABCSG Trial 6, which compared 5 years of adjuvant tamoxifen (40 mg daily for the first 2 years, then 20 mg daily thereafter) with 5 years of adjuvant tamoxifen (40 mg daily for the first 2 years, then 20 mg daily thereafter) plus aminoglutethimide (250 mg daily for week 1, 375 mg daily for week 2, then 500 mg daily thereafter for the first 2 years of treatment) (13) (Fig. 1).

Patients who were eligible for ABCSG Trial 6 (and, therefore, for ABCSG Trial 6a) were postmenopausal women in Austria with surgical treatment for histologically confirmed, endocrine-responsive, primary unilateral stage I or II breast cancer (pT1 to pT3a) with negative or positive axillary nodes. Tumor stage was defined using the TNM (tumor–node–metastasis) classification (14), and postmenopausal status was defined as amenorrhea for at least 1 year or gonadotrophin levels in the postmenopausal range (i.e., a luteinizing hormone concentration of 2–105 pg/mL, a follicle-stimulating hormone concentration of 2–151 pg/mL, and a prostaglandin E2 concentration of 2–210 pg/mL). Surgical treatment consisted of breast-conserving surgery, or modified radical mastectomy with obligatory negative margins plus complete axillary

clearance, including complete level I and II dissection. Patients were required to have had histologic assessment of at least six axillary nodes. Tumors were required to have ER and/or progesterone receptor levels of at least 10 fmol per milligram of cytosol protein by biochemical determination or to be positive by immunohistochemical determination.

Patients were ineligible for both ABCSG Trial 6 and ABCSG Trial 6a if they displayed any evidence of metastatic disease (diagnosed according to local practice by x-ray of the chest wall, native x-ray, computed tomography scan, ultrasound, or other methods) or if they were premenopausal or had a previous diagnosis of malignant disease (except cured squamous cell skin carcinoma and early-stage cervical cancer). Other exclusion criteria included preoperative antineoplastic treatment and irradiation; negative or unknown hormone receptor status; general contraindications including hypersensitivity to tamoxifen or aminoglutethimide; more than 4 weeks between randomization and start of treatment in ABCSG Trial 6a; in situ carcinoma with or without Paget's disease of the nipple; T4 tumor; inflammatory breast cancer; negative or unknown receptor status; deficient patient comprehension and/or reliability; inadequate laboratory parameters; serious concomitant disease rendering treatment impossible as per protocol; age greater than 80 years; Karnofsky Index greater than 3; septic complications; systemic infections; bilateral ovariectomy; or radiotherapy to ovaries.

Adjuvant treatment in ABCSG Trial 6 was initiated within 6 weeks after surgery and lasted for 5 years or until disease recurrence or progression. All patients in ABCSG Trial 6 who had not experienced a recurrence by the end of 5 years of adjuvant therapy were eligible to participate in ABCSG Trial 6a and were randomly reassigned to receive anastrozole (1 mg daily) or no treatment for 3 years, beginning within 6 weeks after completing 5 years of tamoxifen (Fig. 1). We chose a 3-year duration for anastrozole treatment on the basis of financial considerations and on our belief that 3 years of anastrozole should be sufficient to achieve optimal reduction of circulating estrogen levels.

All patients provided written informed consent, and the study was performed in accordance with the Declaration of Helsinki. ABCSG Trials 6 and 6a were approved by the relevant ethics committees in Austria. ABCSG Trial 6a was registered at www.clinicaltrials.gov with number NCT00300508.

Procedures and Assessments

Computer-assisted prerandomization for ABCSG Trial 6a was performed during Trial 6 and centrally at the ABCSG randomization office (Vienna, Austria) and confirmed by the individual trial centers after patient's informed consent was obtained during the ABCSG Trial 6 completion visit. Patients were allocated to receive anastrozole or no further treatment according to the minimization method of Pocock and Simon (15), with stratification by the following prognostic factors: age, tumor size, tumor grade, number of involved nodes, locoregional treatment, adjuvant therapy, hormone receptor status, and participating trial center.

Patients who were randomly assigned to receive no further treatment underwent a physical examination, had laboratory serum parameters and tumor markers assessed, and were monitored for adverse events every 6 months for 5 years (i.e., up to the tenth year after surgery). Adverse events were defined as any adverse change in health or side effect that occurred while the patient was receiving treatment or within a prespecified period after treatment. Serious adverse events were defined as any medical occurrence that results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or clinically significant disability or incapacity, or as a congenital anomaly or birth defect in the children born to women after they participated in this study.

Patients who were randomly assigned to receive anastrozole underwent a physical examination and were monitored for adverse events every 3 months during treatment (i.e., up to the eighth year after surgery) and every 6 months during follow-up (i.e., up to the tenth year after surgery). Laboratory serum parameters and tumor markers were assessed every 3 months during the first year of treatment and every 6 months thereafter. Chest x-ray, abdominal ultrasound, mammography, and gynecologic examinations were performed annually throughout follow-up for both groups.

The primary endpoint for ABCSG Trial 6a was recurrence-free survival, which was defined as the interval between the start of anastrozole treatment or of the observation period (for the no further treatment group) and the first evidence of locoregional recurrence, contralateral breast cancer, or distant metastasis. Locoregional recurrence was defined as recurrence in the ipsilateral breast or chest wall or in the axillary nodes. Distant metastases included all distant lymph node recurrences (i.e., supraclavicular, mammaria internal, and contralateral axilla) and organ metastases. The secondary endpoints were overall survival, which was defined as the interval between the start of anastrozole treatment or of the observation period and death from any cause, and tolerability.

Statistical Analysis

All analyses were performed on an intention-to-treat basis. The effect of treatment on recurrence-free and overall survival was estimated using a univariate Cox proportional hazards regression model (16). A multivariable Cox proportional hazards regression model was also calculated by including all covariates that showed a statistically significant effect in the corresponding univariate analysis at the 5% level. Covariates that did not show a statistically significant effect in the univariate analysis were considered to be irrelevant. Multivariable hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) were calculated. Survival was analyzed by the Kaplan–Meier method using the log-rank test (17). The proportionality assumption of the Cox model was investigated with a time-dependent exploratory variable, which was defined as treatment multiplied by the logarithm (base e) of the time to event (i.e., interaction term). A P value from the Wald chi-squared statistic for this variable of less than 5% would have constituted evidence of a departure from the proportionality assumption. There was no evidence of departure from proportionality at the 5% statistical significance level.

Additional analyses included a multiple Cox proportional hazards regression model that adjusted for the following factors used in the randomization process: age, tumor size, tumor grade, number of involved nodes, locoregional treatment, adjuvant therapy, and hormone receptor status. Interaction terms between treatment and these factors were tested for statistical significance.

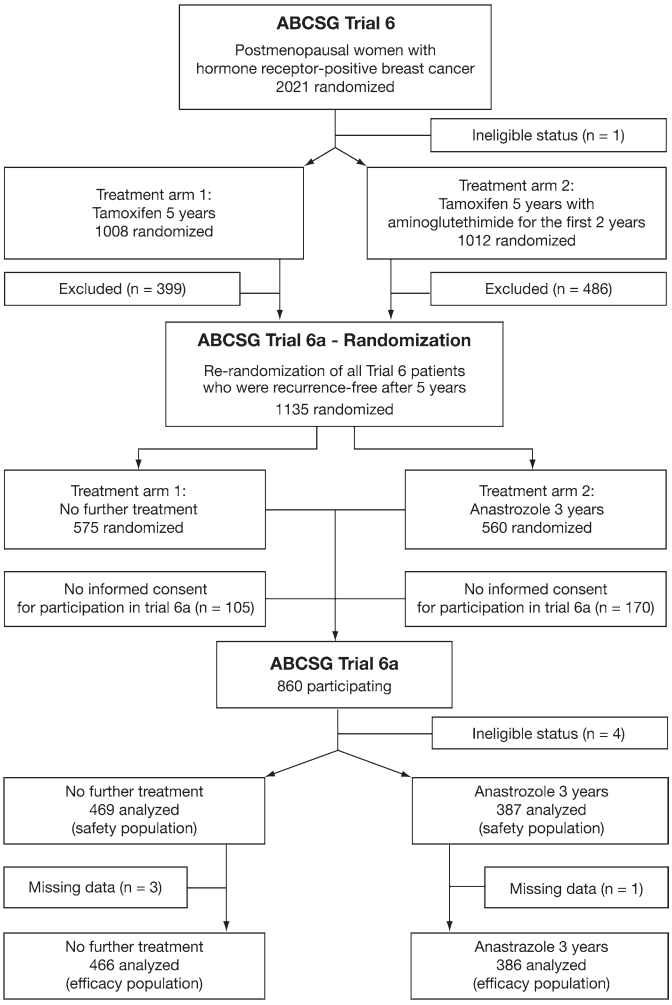

Fig. 1. CONSORT trial flow diagram for Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trials 6 and 6a.

The main analysis of recurrence-free survival included the first occurrence of locoregional cancer, contralateral breast cancer, or distant metastasis as recurrence. In a sensitivity analysis, however, patients who did not experience recurrence were censored at the last follow-up or at the date of diagnosis of a secondary cancer if this type of event occurred first. We estimated that an initial target population of 1700 women was needed for the ABCSG 6a trial to have 85% power at a statistical significance level of 5% to detect a 30% reduction in recurrence with anastrozole.

Adverse events were only counted once per patient at the time they first occurred and are described by their absolute frequencies and proportions. Differences in adverse event rates were estimated with odds ratios and corresponding 95% confidence intervals from logistic regression analysis.

All *P* values are two-sided and were considered to be statistically significant if less than .05. All statistical analyses were performed using SAS software (version 8.02; SAS Institute Inc., Cary, NC).

Results

Patients

Fig. 1 shows the flow of patients through ABCSG Trials 6 and 6a. A total of 1135 women from ABCSG Trial 6 were eligible for randomization in ABCSG Trial 6a; 575 women were randomly assigned to receive no further treatment, and 560 women were randomly assigned to receive 3 years of anastrozole. A total of 860 women (470 of the 575 women randomly assigned to no further treatment and 390 of the 560 women randomly assigned to 3 years of anastrozole) gave written informed consent for entry into Trial 6a. Four women (one in the no further treatment group and three in the anastrozole group) were ineligible for analysis because of liver metastases, hysterectomy, malignant melanoma, and undetermined menopausal status. Of the 856 women eligible for analysis (of whom 469 were randomly assigned to no further treatment and 387 to anastrozole), 406 (47.4%) had received tamoxifen plus aminoglutethimide and 450 (52.6%) had received tamoxifen alone as adjuvant treatment in Trial 6 (Table 1). These 856 women were included in analyses of demographic characteristics, serious adverse events, and predefined adverse events. The imbalance in number of women in the two arms of ABCSG Trial 6a occurred because prerandomization for Trial 6a was performed during ABCSG Trial 6, whereas patients' consent for Trial 6a was confirmed at the completion of ABCSG Trial 6 to prevent any gap in treatment between the completion of treatment in ABCSG Trial 6 and the commencement of ABCSG Trial 6a. Finally, because of missing data in ABCSG Trial 6a, 466 women in the no further treatment arm and 386 women in the anastrozole arm were available for primary outcome assessments (total n = 852).

Demographic data and disease characteristics for patients in ABCSG Trial 6a are shown in Table 1. At prerandomization for Trial 6a, the median age of the patients was 68.1 years (range = 51.8–85.5 years). Median follow-up at this analysis was 62.3 months.

Efficacy

Women who received 3 years of anastrozole as extended adjuvant therapy experienced statistically significantly fewer recurrences (i.e., a first occurrence of locoregional, contralateral, or distant metastatic events) than women who received no extended adjuvant treatment; these women had a 38% reduced risk of recurrence (HR = 0.62, 95% CI = 0.40 to 0.96, *P* = .031) (Table 2). The recurrence rate was 11.8% for patients in the no further treatment group at 10 years after surgery, compared with 7.1% for patients receiving adjuvant treatment with anastrozole. Kaplan–Meier curves for recurrence-free survival are presented in Fig. 2.

The incidence of recurrence events is shown in Table 2. The difference in assessment intervals between the two groups had no effect on the total hazard ratio of events (data not shown). When the recurrence events were considered separately by type, only the incidence of distant metastatic events differed statistically significantly between the study arms (35 events for the no further treatment arm versus 16 events for the anastrozole arm; HR = 0.53, 95% CI = 0.29 to 0.96, *P* = .034). The Kaplan–Meier curves for distant metastatic recurrence–free survival began to separate at approximately 20 months, revealing an advantage for the women who received anastrozole (Fig. 3). In addition, the incidence of recurrence events in Trial 6a was lower in patients who had received tamoxifen plus aminoglutethimide in ABCSG Trial 6 (32 events in 404 patients) than in patients who had received tamoxifen alone (55 events in 448 patients) (HR = 0.64, 95% CI = 0.41 to 0.98; *P* = .042).

Table 1. Demographic and disease characteristics of patients enrolled in ABCSG Trial 6a*

Characteristic	No further treatment (n = 469)	3 y of anastrozole (n = 387)
Median age, y (range)	68.5 (51.8–85.5)	67.8 (51.8–83.2)
Involved nodes, No. (%)		
None	323 (68.9)	255 (65.9)
1–3	112 (23.9)	104 (26.9)
4–10	27 (5.8)	22 (5.7)
>10	7 (1.5)	6 (1.6)
Tumor size†, No. (%)		
T1	296 (63.1)	241 (62.3)
T2	166 (35.4)	137 (35.4)
T3	7 (1.5)	9 (2.3)
Tumor grade‡, No. (%)		
G1	86 (18.3)	60 (15.5)
G2	256 (54.6)	220 (56.8)
G3	92 (19.6)	79 (20.4)
Gx	35 (7.5)	28 (7.2)
Primary therapy, No. (%)		
Breast-conserving surgery	266 (56.7)	222 (57.4)
Modified radical mastectomy	203 (43.3)	165 (42.6)
Pretreatment§, No. (%)		
Tamoxifen alone	240 (51.2)	210 (54.3)
Tamoxifen plus aminoglutethimide	229 (48.8)	177 (45.7)
ER/PgR status, No. (%)		
Positive/positive	359 (76.5)	309 (79.8)
Positive/negative	87 (18.6)	52 (13.4)
Negative/positive	8 (1.7)	10 (2.6)
ER or PgR status unknown	15 (3.2)	16 (4.1)

* ABCSG = Austrian Breast and Colorectal Cancer Study Group; ER = estrogen receptor; PgR = progesterone receptor.

† T1 = 0 to ≤2 cm; T2 > 2 to ≤5 cm; T3 > 5 cm.

‡ G1 = well differentiated; G2 = moderately differentiated; G3 = poorly differentiated; Gx = unknown differentiation.

§ Adjuvant treatment received in ABCSG Trial 6.

The forest plot in Fig. 4 shows the risk of recurrence stratified by age, nodal status, tumor grade, hormone receptor status, and type of adjuvant therapy received in ABCSG Trial 6. This subgroup analysis demonstrated that among patients with ER-positive, PgR-positive tumors (664/852), those who received anastrozole had a lower risk of recurrence than those who received no further treatment (HR = 0.32, 95% CI = 0.18 to 0.58, $P<.001$). The hazard ratios of recurrence calculated for patients who received tamoxifen only versus tamoxifen plus aminoglutethimide are based on comparable numbers of patients and suggest a statistically significantly better outcome, in terms of recurrence risk, for patients who did not receive aminoglutethimide during their adjuvant therapy in ABCSG Trial 6 (HR = 0.40, 95% CI = 0.22 to 0.73, $P = .002$). This subgroup analysis also suggests that among a small number of patients with ER-positive, PgR-negative tumors (139/852), those who received anastrozole had a greater risk of recurrence than those who received no further treatment (HR = 3.49, 95% CI = 1.31 to 9.30, $P = .008$).

Despite the improvement in recurrence-free survival, there was no statistically significant difference in overall survival between study arms (55 deaths [11.7%] for the no further treatment arm versus 40 deaths [10.3%] for the anastrozole arm; HR of death from any cause = 0.89, 95% CI = 0.59 to 1.34, $P = .570$). In the no further treatment arm, 25 deaths were breast cancer–related and 30 were due to other causes. In the anastrozole arm, 12 deaths were breast cancer–related and 28 were due to other causes.

Overall, 237 women withdrew from ABCSG Trial 6a before the 3-year period ended (128 [33.1%] from the anastrozole group and 109 [23.2%] from the control group). Adverse events accounted for 45 withdrawals from the anastrozole arm of the trial (two of these withdrawals were also due to recurrence) but for none of the withdrawals from the no further treatment arm. There were 25 and 42 withdrawals due to disease recurrence or the appearance of a secondary tumor in the anastrozole arm and no further treatment arm, respectively, and eight and six additional deaths, respectively.

Tolerability

Overall, 13 serious adverse events occurred during ABCSG Trial 6a (seven in the anastrozole arm and six in the no further treatment arm) (Table 3). Of these events, only one in the anastrozole arm (fracture) was considered by the investigators as being related to study treatment.

The incidences of predefined adverse events by treatment group are shown in Table 4. Anastrozole therapy was well tolerated, and the adverse events that were experienced by patients were as expected in view of available anastrozole tolerability data. All of the adverse events occurred more frequently in patients treated with anastrozole than in patients who received no further treatment. The differences between the study arms were highly statistically significant ($P<.001$) for hot flushes; asthenia, somnolence; allergy, cutaneous toxicity, skin rash; hair loss; and nausea (all grade 1 toxic effects).

Discussion

Our data show that extended adjuvant therapy with 3 years of anastrozole after successful completion of 5 years of tamoxifen statistically

Table 2. Incidence of recurrence events in ABCSG Trial 6a at 5 years*

Event	No further treatment (n = 466), No. (%)	3 y of anastrozole (n = 386), No. (%)	Total (n = 852), No. (%)	HR (95% CI)	P†
Total	57 (12.2)	30 (7.8)	87 (10.2)	0.62 (0.40 to 0.96)	.031
Locoregional	15 (3.2)	10 (2.6)	25 (2.9)	0.79 (0.36 to 1.76)	.564
Distant metastatic	35 (7.5)	16 (4.1)	51 (6.0)	0.53 (0.29 to 0.96)	.034
Contralateral breast cancer	11 (2.4)	6 (1.6)	17 (2.0)	0.67 (0.25 to 1.80)	.422

* ABCSG = Austrian Breast and Colorectal Cancer Study Group; HR = hazard ratio; CI = confidence interval.

† Data analyzed using Cox proportional hazards regression model with two-sided *P* values.

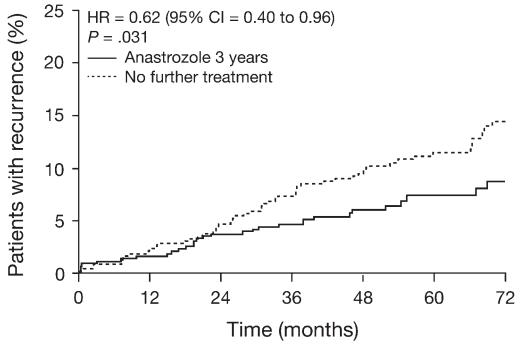

Fig. 2. Kaplan–Meier curves for recurrence-free survival in the anastrozole and no further treatment arms of Austrian Breast and Colorectal Cancer Study Group Trial 6a. In total, 852 women were analyzed for the primary efficacy outcome. HR = hazard ratio; CI = confidence interval.

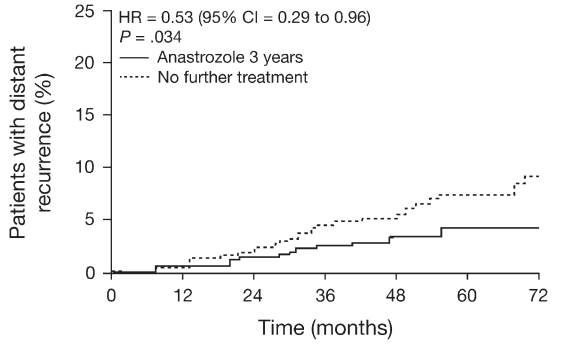

Fig. 3. Kaplan–Meier curves for distant metastatic recurrence–free survival in the anastrozole and no further treatment arms of Austrian Breast and Colorectal Cancer Study Group Trial 6a. HR = hazard ratio; CI = confidence interval.

significantly reduced the risk of recurrence by 38% compared with no further treatment. This finding is in accordance with results of the larger MA.17 trial, in which women who received 5 years of letrozole after 5 years of adjuvant tamoxifen experienced a 42% reduction in the risk of recurrence compared with women who received placebo (12). Our data indicate that extended adjuvant endocrine therapy with anastrozole is a valid therapeutic option for breast cancer patients who have completed 5 years of adjuvant tamoxifen. Furthermore, with a median follow-up of more than 5 years, these data can be considered to be mature.

A potential study limitation is that prerandomization is not standard practice. We chose to randomly assign all eligible patients in ABCSG Trial 6 (i.e., all those who remained in the trial and disease free) to an arm of Trial 6a to ensure that there would be no gap in treatment between completion of 5 years of primary adjuvant therapy (ABCSG Trial 6) and commencement of the extended study (ABCSG Trial 6a). However, the number of patients in the prerandomized treatment groups who gave consent for Trial 6a differed between the groups. In almost all cases, the decision not to enter Trial 6a was because the patient felt that 5 years of adjuvant treatment was sufficient. Very few patients became ineligible because they experienced an event between the time of the central randomization and the final visit for Trial 6. However, the baseline characteristics for the anastrozole and no further treatment groups were well balanced, which suggests that prerandomization did not cause sufficient bias to invalidate the study conclusions.

No conclusion should be drawn regarding our observation of an apparent improvement in outcome for ER-positive and PgR-positive patients compared with ER-positive and PgR-negative

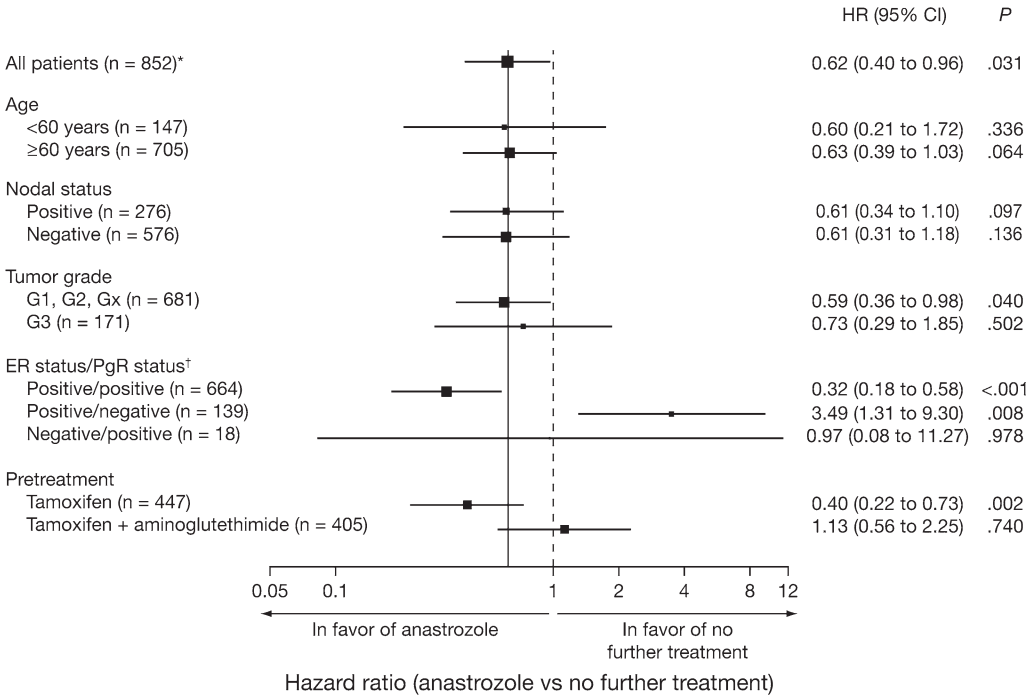

Fig. 4. Forest plot of risk of recurrence stratified by subgroups. The **squares** represent the point estimate of the hazard ratio (HR), the **lines** are the 95% confidence intervals (CIs), and the size of the **square** is proportional to the precision of the estimate (number of patients, number of events, and variance). The **vertical dashed line** indicates the no effect point, and the **solid vertical line**, the overall treatment effect. * = Data for four patients were missing at the time of the analysis; † = ER/PgR status is unknown in 31 patients; ER = estrogen receptor; PgR = progesterone receptor.

Table 3. Incidence of serious adverse events during ABCSG Trial 6a*

Serious adverse event	No further treatment (n = 469)	3 y of anastrozole (n = 387)
Fractures, No. (%)	5 (1.1)	3 (0.8)
Thrombosis, No. (%)	1 (0.2)	2 (0.5)
Embolism, No. (%)	0	1 (0.3)
Myocardial infarction, No. (%)	0	1 (0.3)

* ABCSG = Austrian Breast and Colorectal Cancer Study Group.

patients because of the very small number of patients in the latter group. The same applies to the finding that extended anastrozole treatment provided no additional benefit for women who had received aminoglutethimide as part of their adjuvant therapy compared with those who had not. Subgroup analysis should be interpreted with caution and can lead to a substantial amount of misinterpretation because it is frequently based on small numbers and thus has low statistical power. For example, in some small subgroups in the MA.17 trial, a benefit was seen for patients treated with placebo compared with those who received extended adjuvant letrozole treatment (12). In addition, other studies that have examined the effect of aromatase inhibitor treatment in subgroups of patients according to receptor status have suggested that there is no real difference in treatment effect according to receptor status (18,19).

The results from ABCSG Trial 6 showed no statistically significant difference in 5-year disease-free survival for adjuvant treatment with tamoxifen plus aminoglutethimide compared with tamoxifen alone (13), indicating that 2 years of this combined adjuvant therapy did not improve the prognosis of patients compared with tamoxifen monotherapy. However, it is possible that prior exposure to the aromatase inhibitor aminoglutethimide in ABCSG Trial 6 may have, to some extent, reduced the efficacy of subsequent therapy with a second aromatase inhibitor (anastrozole) in this study. Breast carcinomas can develop resistance to the estrogen-deprived environment created by aromatase inhibitor treatment (20), which may explain the difference in the risk of recurrence seen between adjuvant pretreatment populations in the Trial 6a subgroup analysis. In this context, it is interesting that data from patients with advanced breast cancer suggest that nonsteroidal aromatase inhibitors can have a clinical benefit (defined as complete responses, partial responses, and disease stabilization for at least 24 weeks) after disease progression occurs during treatment with a steroidal aromatase inhibitor (21). However, our data cannot provide a detailed assessment of the effect of prior aminoglutethimide therapy on the efficacy of subsequent aromatase inhibitor treatment because ABCSG Trial 6a did not examine this comparison. The lower incidence of recurrence events in Trial 6a in patients who had received tamoxifen plus aminoglutethimide in ABCSG Trial 6 versus in those who had received tamoxifen alone could reflect a carryover effect of aminoglutethimide in Trial 6. However, there

Table 4. Incidence of predefined adverse events during ABCSG Trial 6a*

				Cumulative data for grade 1–4 and 2–4 adverse events†			
Adverse event	Grade	No further treatment (n = 469), No. (%)	3 years of anastrozole (n = 387), No. (%)	No further treatment (n = 469), No. (%)	3 years of anastrozole (n = 387), No. (%)	OR (95% CI)	*P*
Hot flushes	1	105 (22.4)	151 (39.0)	105 (22.4)	151 (39.0)	2.44 (1.80 to 3.31)	<.001
Asthenia, somnolence	1	8 (1.7)	20 (5.2)	20 (4.3)	41 (10.6)	2.82 (1.62 to 4.90)	<.001
	2	11 (2.3)	15 (3.9)	12 (2.6)	21 (5.4)	2.30 (1.12 to 4.75)	.02
	3	1 (0.2)	3 (0.8)				
	4	0 (0.0)	3 (0.8)				
Allergy, cutaneous toxicity, skin rash	1	5 (1.1)	17 (4.4)	8 (1.7)	29 (7.5)	4.93 (2.23 to 10.93)	<.001
	2	3 (0.6)	7 (1.8)	3 (0.6)	12 (3.1)	5.23 (1.47 to 18.69)	.011
	3	0 (0.0)	4 (1.0)				
	4	0 (0.0)	1 (0.3)				
Hair loss	1	8 (1.7)	19 (4.9)	10 (2.1)	35 (9.0)	4.83 (2.36 to 9.90)	<.001
	2	2 (0.4)	11 (2.8)	2 (0.4)	16 (4.1)	10.61 (2.42 to 46.43)	.002
	3	0 (0.0)	5 (1.3)				
Diarrhea	1	5 (1.1)	7 (1.8)	12 (2.6)	16 (4.1)	1.73 (0.81 to 3.70)	.159
	2	7 (1.5)	7 (1.8)	7 (1.5)	9 (2.3)	1.65 (0.61 to 4.48)	.32
	3	0 (0.0)	1 (0.3)				
	4	0 (0.0)	1 (0.3)				
Nausea	1	10 (2.1)	17 (4.4)	11 (2.3)	32 (8.3)	3.97 (1.97 to 7.99)	<.001
	2	1 (0.2)	11 (2.8)	1 (0.2)	15 (3.9)	19.88 (2.61 to 151.24)	.004
	3	0 (0.0)	3 (0.8)				
	4	0 (0.0)	1 (0.3)				
Vaginal bleeding	1	1 (0.2)	1 (0.3)	1 (0.2)	3 (0.8)	3.84 (1.40 to 37.06)	.245
	2	0 (0.0)	2 (0.5)	0 (0.0)	2 (0.5)	–	–
Vaginal discharge	1	13 (2.8)	23 (5.9)	13 (2.8)	23 (5.9)	2.34 (1.17 to 4.68)	.017
Vaginal dryness	1	32 (6.8)	45 (11.6)	32 (6.8)	45 (11.6)	1.90 (1.18 to 3.07)	.008
Bone pain (including joint pain)	1	86 (18.3)	95 (24.5)	86 (18.3)	95 (24.5)	1.55 (1.11 to 2.17)	.009

* ABCSG = Austrian Breast and Colorectal Cancer Study Group; OR = odds ratio; CI = confidence interval; – = not applicable.

† Odds ratios on the same line as grade 1 event include all adverse events; those on the same line as grade 2 events include grade 2–4 adverse events.

was no statistically significant difference in disease-free survival between therapy arms in Trial 6 (13).

We cannot draw firm conclusions from the trends indicated in the ABCSG Trial 6a subgroup analysis without further investigation in prospectively designed clinical trials. Because aminoglutethimide is no longer commonly used in the adjuvant setting, such studies are unlikely to be initiated. However, these efficacy data indicate that it may be appropriate to investigate the effects of giving a different aromatase inhibitor in the extended adjuvant setting from that given as adjuvant therapy.

The tolerability profile of anastrozole observed in ABCSG Trial 6a is consistent with that observed in the 68-month completed treatment analysis of the ATAC trial (7). The low incidence of fractures in both arms of this study may reflect the protective effect of 5 years of tamoxifen on bone health (22).

The impact of our data on current practice is unclear. However, the introduction of an aromatase inhibitor following adjuvant therapy with tamoxifen has been addressed in an American Society of Clinical Oncology technology assessment on adjuvant use of aromatase inhibitors (23), which recommends the use of the aromatase inhibitor "that has been studied in the setting most closely approximating any individual patient's clinical circumstance." To date, anastrozole has shown superiority over tamoxifen in both the primary adjuvant and switched adjuvant settings (i.e., completion of the 5-year adjuvant treatment period with an aromatase inhibitor rather than continuing with tamoxifen after 2 years of treatment) (7–9,11). In addition, the data presented here highlight the potential of anastrozole for use in the extended adjuvant setting. More mature data are awaited for the primary adjuvant setting with anastrozole (ATAC trial) and for the primary adjuvant and sequencing settings with letrozole (BIG 1–98 trial). To date, the only data available for exemestane are in the switched adjuvant setting from the Intergroup Exemestane Study at a mean follow-up of 55.7 months (24). Therefore, of the three third-generation aromatase inhibitors, anastrozole currently has the most comprehensive dataset relating to adjuvant therapy.

The apparent benefit of extended adjuvant therapy with aromatase inhibitors raises the question of the optimal duration of adjuvant endocrine treatment with aromatase inhibitors. This question is being addressed by the ongoing Secondary Adjuvant Long-term Study with Arimidex study, which compares 2 years with 5 years of extended adjuvant anastrozole after 5 years of exposure to adjuvant endocrine therapy (current recruitment exceeds 2000 patients). The more manageable side effect profile of anastrozole compared with tamoxifen may allow the duration of adjuvant treatment to extend beyond the 5-year period recommended for tamoxifen. Consequently, we may now be in a position to investigate the possibility of tailoring the duration of adjuvant treatment to the requirements of individual patients or disease types.

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