

Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial



Raimund Jakesz, Walter Jonat, Michael Gnant, Martina Mittlboeck, Richard Greil, Christoph Tausch, Joern Hilfrich, Werner Kwasny, Christian Menzel, Hellmut Samonigg, Michael Seifert, Guenther Gademann, Manfred Kaufmann, on behalf of the ABCSG and the GABG*

Summary

Background Tamoxifen has been the standard adjuvant treatment for postmenopausal women with hormone-responsive early breast cancer for more than 20 years. However, the third-generation aromatase inhibitor anastrozole has proven efficacy and tolerability benefits compared with tamoxifen when used as initial adjuvant therapy. We investigate whether women who have received a period of adjuvant tamoxifen would benefit from being switched to anastrozole.

Methods We present a combined analysis of data from two prospective, multicentre, randomised, open-label trials with nearly identical inclusion criteria. Postmenopausal women with hormone-sensitive early breast cancer who had completed 2 years' adjuvant oral tamoxifen (20 or 30 mg daily) were randomised to receive 1 mg oral anastrozole (n=1618) or 20 or 30 mg tamoxifen (n=1606) daily for the remainder of their adjuvant therapy. The primary endpoint was event-free survival, with an event defined as local or distant metastasis, or contralateral breast cancer. Analysis was by intention to treat.

Findings 3224 patients were included in analyses. At a median follow-up of 28 months, we noted a 40% decrease in their risk for an event in the anastrozole group as compared with the tamoxifen group (67 events with anastrozole vs 110 with tamoxifen, hazard ratio 0.60, 95% CI 0.44–0.81, p=0.0009). Both study treatments were well tolerated. There were significantly more fractures (p=0.015) and significantly fewer thromboses (p=0.034) in patients treated with anastrozole than in those on tamoxifen.

Interpretation These data lend support to a switch from tamoxifen to anastrozole in patients who have completed 2 years' adjuvant tamoxifen.

Introduction

Breast cancer is the most common female cancer. It is diagnosed in more than a million women worldwide and accounts for more than 400 000 deaths yearly. More than 110 cases per 100 000 of the population are diagnosed in Germany and Austria every year.¹ The incidence of breast cancer increases with age, and about three-quarters of the women affected are postmenopausal. In these individuals, about 80% of tumours are hormone-receptor positive.²

For more than 20 years, the anti-oestrogen tamoxifen has been the established endocrine adjuvant therapy after surgery for postmenopausal women with early breast cancer. 5 years is generally judged the optimum duration for treatment,³ since tamoxifen therapy beyond 5 years seems to confer no extra benefit in terms of disease-free survival.^{4,5} However, several side-effects are inherent with long-term tamoxifen treatment. The partial oestrogenic activity of tamoxifen in some tissues leads to an increased risk of endometrial cancer and thromboembolic events over the course of treatment.^{6–8} Tamoxifen resistance can also develop.⁹ The 5-year standard for adjuvant

tamoxifen therapy, therefore, seems to be imposed by the limitations of the drug rather than by the optimum duration of therapy. In particular, the relapse pattern for low-risk and intermediate-risk tumours indicates that adjuvant treatment should continue after 5 years, with overview results suggesting that there is a 1.5–2% yearly risk of recurrence of breast cancer in years 5–15 after initial diagnosis.^{10,11}

The 15-year outcome of some oestrogen-receptor positive tumours might be worse than that of oestrogen-receptor negative lesions.¹² The administration of tamoxifen beyond the optimum time of efficacy might, therefore, result in side-effects without a concomitant therapeutic benefit.

The limitations of tamoxifen have led to a search for alternative endocrine therapies with increased efficacy and fewer long-term complications. The third-generation aromatase inhibitors anastrozole, letrozole, and exemestane are highly selective for aromatase and inhibit 97–99% of oestrogen synthesis from this source.^{13,14} Results of trials such as the ATAC study¹⁵ have shown the improved efficacy and tolerability of anastrozole over tamoxifen, and data now support the

Lancet 2005; 366: 455–62

*Study groups listed at end of report

See [Comment](#)

Austrian Breast and Colorectal Cancer Study Group (ABCSG), Vienna Medical University, Vienna General Hospital, Waehringer Guertel 18-20, Vienna A-1090, Austria (Prof R Jakesz MD, Prof M Gnant MD, Prof M Mittlboeck PhD, Prof R Greil MD, C Tausch MD, W Kwasny MD, Prof C Menzel MD, Prof H Samonigg MD, Prof M Seifert MD); and German Adjuvant Breast Cancer Group (GABG), University of Frankfurt, Frankfurt am Main, Germany (Prof W Jonat MD, Prof J Hilfrich MD, Prof G Gademann MD, Prof M Kaufmann MD)

Correspondence to: Prof Raimund Jakesz raimund.jakesz@meduniwien.ac.at

use of 5 years' anastrozole as adjuvant therapy for postmenopausal women with early breast cancer. However, tamoxifen is still a useful and ubiquitous treatment option, and by employing a strategy of switching therapy from tamoxifen to an aromatase inhibitor, the unnecessary longer-term side-effects of tamoxifen might be obviated and the complications of long-term tamoxifen therapy avoided. Data indicate a positive effect on recurrence-free survival when switching from tamoxifen to an aromatase inhibitor.^{16,17}

The most recent technical assessment from the American Society of Clinical Oncology (ASCO)¹⁸ recommends that optimum adjuvant therapy for postmenopausal women should now include the use of an aromatase inhibitor, either as initial treatment or after 2–5 years' treatment with tamoxifen, to reduce the risk of tumour recurrence. The aim of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) trial 8/Arimidex-Nolvadex (ARNO) 95 combined analysis was to assess whether switching to anastrozole after 2 years' tamoxifen treatment is more effective than the standard 5 years' adjuvant tamoxifen therapy.

Methods

Patients

This study is a prospectively-planned, event-driven combined analysis of two trials—ABCSG trial 8 and the ARNO 95 trial by the German Adjuvant Breast Cancer Group (GABG)—both of which were prospective, multicentre, randomised, open-label studies and had broadly similar inclusion criteria and outcome measures.

Eligible patients were postmenopausal women aged 80 years or younger (ABCSG trial 8) or 75 years or younger (ARNO 95) with histologically verified, locally radically treated invasive or minimally invasive breast cancer without previous chemotherapy, hormone therapy, or radiotherapy. Postmenopausal status was assumed for patients whose last menstruation took place at least 12 months before study entry, for those who had undergone bilateral ovariectomy, or for whom follicle-stimulating hormone and luteinising hormone concentrations indicated postmenopausal status. All patients had endocrine-responsive tumours—ie, with concentrations of oestrogen receptors or progesterone receptors of more than 10 fmol/mg cytosol protein, or were oestrogen-receptor or progesterone-receptor positive as assessed histochemically. ABCSG trial 8 included patients with G1 and G2 ductal carcinoma and Gx lobular tumours, whereas patients with ductal carcinoma of any grade were recruited to ARNO 95. Tumours were graded according to the Bloom and Richardson scale in both studies.¹⁹

Inclusion criteria common to both trials were absence of preoperative chemotherapy, hormone therapy, or radiotherapy, tumour infiltration of up to ten (ABCSG trial 8) or nine (ARNO 95) lymph nodes, and absence of organ metastases. Exclusion criteria across both trials were indeterminate menopausal status (or menopausal status maintained by medication), presence of secondary malignant disease, tumour infiltration of skin or breast muscle (T4 tumours), and presence of other concomitant serious medical conditions—eg, those involving bone marrow function, the central nervous system, uncompensated cardiac insufficiency, or uncontrolled local or systemic infection. Although hormone replacement therapy was not excluded in the protocol, it was considered as explicitly contraindicated in both countries for patients receiving adjuvant breast cancer treatment.

Eligible patients underwent modified radical mastectomy or breast-conserving surgery with axillary lymph-node dissection or sentinel lymph-node biopsy (with or without subsequent radiotherapy), followed by adjuvant tamoxifen therapy started within 6 weeks (ABCSG trial 8) or 4 weeks (ARNO 95) of surgery or radiotherapy, where applicable.

For both studies, patients had to complete 2 years' adjuvant oral tamoxifen therapy in accordance with local guidelines (20 mg daily for ABCSG trial 8, and 20 mg or 30 mg daily for ARNO 95; patients administered 30 mg continued on that dose unless otherwise indicated). Women were randomised before beginning treatment with tamoxifen in ABCSG trial 8 and within 2 years of tamoxifen treatment in ARNO 95. The accrual period for this combined analysis was January, 1996, to August, 2003. Since the randomisation processes in Austria and Germany differed, the timepoint of 2 years post-surgery was used as a starting point for this analysis.

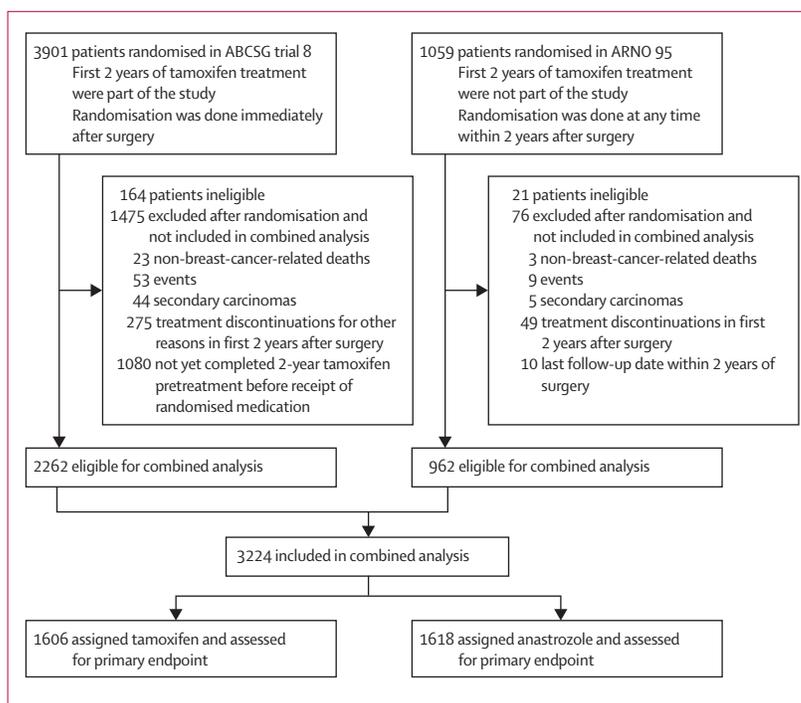


Figure 1: Trial profile

All patients provided written informed consent and both studies were done in accordance with the Declaration of Helsinki. ABCSG trial 8 and ARNO 95 were approved by the relevant ethics committees in Austria and Germany, respectively.

Procedures

Randomisation for ABCSG trial 8 was done centrally at the ABCSG randomisation centre, Vienna, Austria. Randomisation for ARNO 95 was done at the Department of Medical Biometry and Statistics, Freiburg, Germany. The computer-assisted randomisation schedules for ABCSG trial 8 were based on minimisation as a dynamic algorithm designed to counteract imbalance between treatments, taking stratification factors into account. For ARNO 95, these schedules were based on block randomisation. Patients were randomised to either continue tamoxifen or to switch to oral anastrozole (1 mg per day) for 3 years after completion of 2 years' adjuvant therapy. In Austria, this randomisation was done within 6 weeks after surgery, whereas in Germany it was done at any time between surgery and 6 weeks after completion of the first 2 years' adjuvant therapy.

Patients received a physical examination and were monitored for safety and tolerability. Case report forms were provided for documentation and adhered to as per protocol. In Austria, the monitoring took place at 3-monthly intervals throughout the first year of randomised therapy, at 6-monthly intervals in the second and third year, and yearly thereafter. In Germany, assessment of patients was done at 6-monthly intervals. There were no observation-free intervals. Gynaecological examinations, thoracic X-rays, skeletal scintigraphy, and abdominal sonography, liver ultrasound, and standard mammography were done as appropriate (at least yearly) to identify the presence of disease recurrence (locoregional, contralateral, or distant metastatic tumour [lymph node or organ]). The assessments done at each visit were common to, and the number of patients with data was similar in, both treatment groups. Events were confirmed histologically, cytologically, or, where not clinically obvious, by the various radiological screening methods used at the regular assessments.

The primary endpoint was event-free survival, defined as time to relapse at any site or incidence of contralateral breast cancer. Distant recurrence-free survival and tolerability issues were also compared.

Statistical analysis

In Austria, patients were allocated to the treatment groups according to the method of Pocock and Simon,²⁰ stratifying for the following prognostic factors: age, tumour grade, tumour stage, nodal status, and participating centres grouped into federal states. In Germany, only the participating centre was considered

during randomisation. For the common analysis, we calculated that 278 events would be required for the final analysis to detect a hazard ratio (HR) of 0.7 for event-free survival between the treatment groups with a power of 80% and a two-sided significance level of 0.05. Interim analyses were planned on reaching 139 and 209 events, using a significance level of 0.001 (stopping boundary) to maintain a significance level of 0.05 for the final analysis. The number of events needed to trigger the first interim analysis was reached in April, 2004 (143 observed events). The Steering Committee decided to reassess all data for accuracy. As the stopping boundary for event-free survival was reached at this analysis, the independent data monitoring committee decided, in November, 2004, to recommend close of recruitment and to publish the combined analysis data.

Analyses were by intention to treat. Data are presented in Kaplan-Meier curves,²¹ and tested by log-rank tests.^{22,23} HRs and their corresponding 95% CIs were estimated by the proportional-hazards regression model of Cox.²⁴ Main analyses were based on the first corresponding event per patient. In additional sensitivity analyses, first events only were considered. Thus, for analysis of distant recurrence-free survival, the first observed distant metastasis was included in the main analysis. In the sensitivity analysis, however, patients who did not have a distant metastasis as first cancer-related event—eg, secondary cancer, locoregional event, or contralateral event—were censored at the first observed event.

All analyses were done with SAS (version 8.02). Adverse events were only counted once per patient, and

	Tamoxifen (n=1606)	Anastrozole (n=1618)
Age at surgery (years; median, range)	62.0 (41.4–80.0)	62.3 (46.0–80.3)
Affected nodes		
None	1188 (74%)	1201 (74%)
1–3	358 (22%)	346 (21%)
4–9	59 (4%)	70 (4%)
Unknown	1 (<1%)	1 (<1%)
Tumour size		
T1	1119 (70%)	1136 (70%)
T2	464 (29%)	463 (29%)
T3	21 (1%)	18 (1%)
Unknown	2 (<1%)	1 (<1%)
Tumour grade		
G1, G2, Gx	1504 (94%)	1540 (95%)
G3	91 (6%)	76 (5%)
Unknown	11 (<1%)	2 (<1%)
Surgery		
Breast-conserving surgery	1242 (77%)	1236 (76%)
Radical modified mastectomy	362 (23%)	382 (24%)
Unknown	2 (<1%)	0
Hormone receptor status		
ER-positive/PgR-positive	1247 (78%)	1272 (79%)
ER-positive/PgR-negative	281 (18%)	283 (18%)
ER-negative/PgR-positive	39 (2%)	28 (2%)
Unknown	39 (2%)	35 (2%)

Data are number (%) unless otherwise indicated. ER=oestrogen receptor; PgR=progesterone receptor.

Table 1: Baseline characteristics

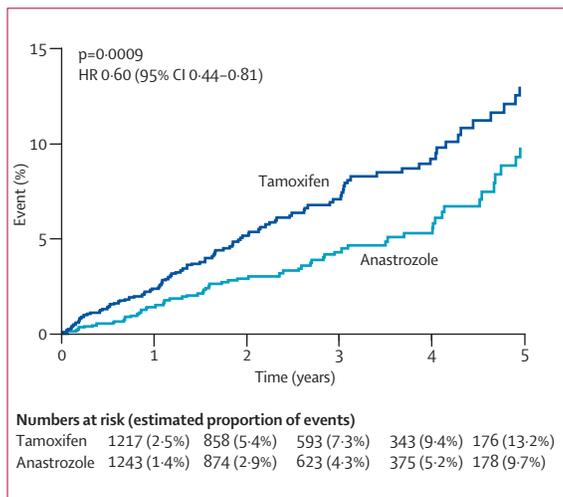


Figure 2: Kaplan-Meier curves of event-free survival
 0 time point=2 years after surgery. SD at 3 years: tamoxifen=0.81, anastrozole=0.65

are described with absolute frequencies and proportions. Differences in the adverse event rates were estimated with exact odds ratios (OR) and corresponding 95% CIs. Exact ORs stratified by country were calculated for the five types of serious adverse events available for Austrian and German patients (myocardial infarct, embolism, thromboses, fractures, and endometrial cancer). The exact calculations were done with StatXact (version 6). All p values are two-sided, and a p less than 0.05 was judged significant.

Role of the funding source

The study designs were developed by the ABCSG and the GABG. The management of the trial has been undertaken by the ABCSG and GABG with funding and organisational support from the trial sponsors: AstraZeneca in Austria and the GABG in Germany. The ABCSG statistician analysed all data. AstraZeneca funded editorial assistance in the form of technical preparation of references, figures, tables, technical editing for English language, formatting of the report to *Lancet* style, and administrative support. AstraZeneca had no role in data interpretation. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. 3224 patients (2262 in ABCSG trial 8 and 962 in ARNO 95) were randomised to either continue tamoxifen (n=1606) or switch to anastrozole (n=1618). Median follow-up was 28 months (95% CI 26–30) after initial treatment with tamoxifen. The treatment groups were well balanced in terms of age, nodal status, tumour stage, tumour grade, oestrogen-receptor and progesterone-receptor status, and previous surgery (table 1). At the time of disclosure of trial data, 882 (55%) patients assigned anastrozole and 884 (55%) assigned tamoxifen had completed 5 years of treatment.

Event-free survival was higher in patients who took anastrozole than in those who continued treatment with

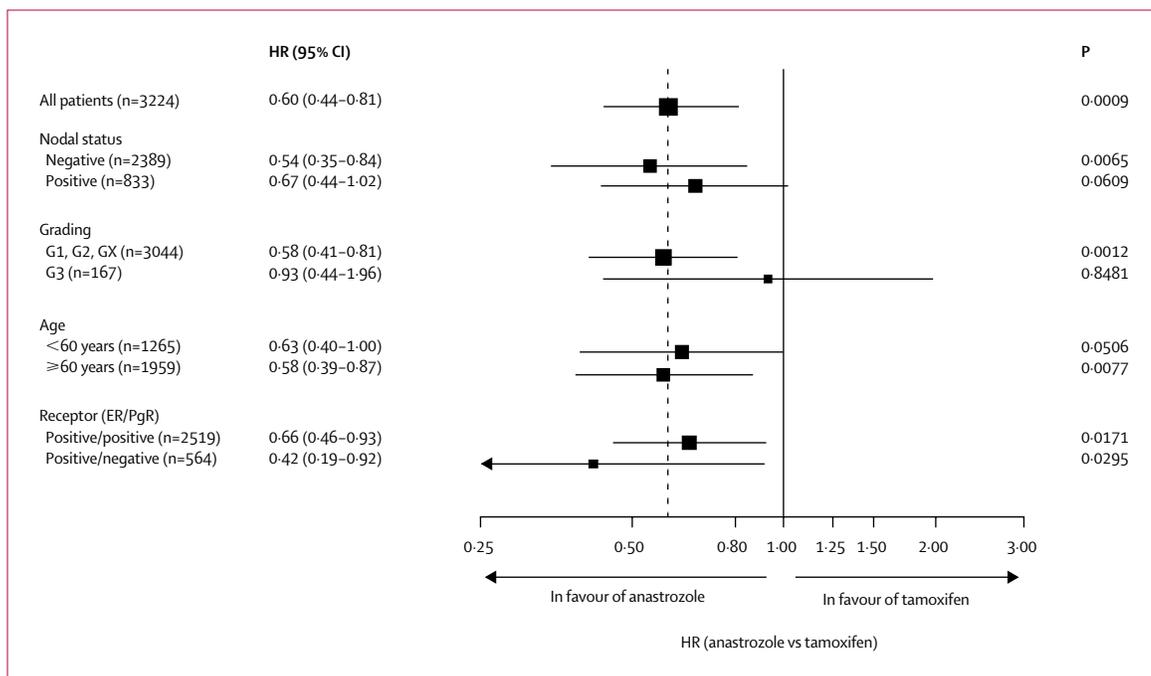


Figure 3: HR (95%CI) for anastrozole versus tamoxifen stratified by nodal status, tumour grade, age, and hormone receptor status
 ER=oestrogen receptor; PgR=progesterone receptor.

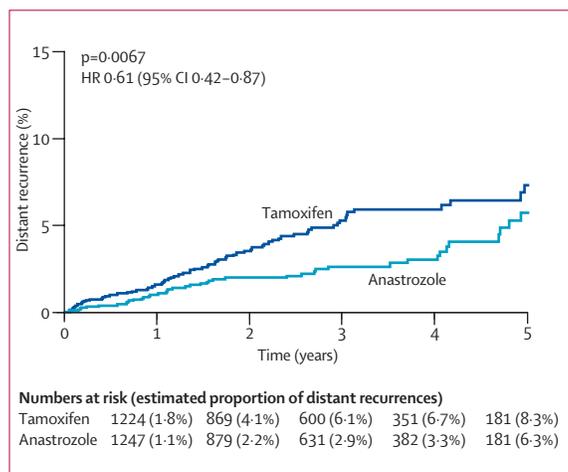


Figure 4: Kaplan-Meier curves of distant recurrence-free survival
0 time point=2 years after surgery. SD at 3 years: tamoxifen=0.76, anastrozole=0.52.

tamoxifen (figure 2). 67 events were noted in the anastrozole group and 110 events in the tamoxifen group. In the combined analysis, there was an HR of 0.60 (95% CI 0.44–0.81, $p=0.0009$) in favour of anastrozole at 3 years post-switch for the occurrence of an event. With respect to first events only, the HR was 0.59 (0.44–0.81, $p=0.0008$). Event-free survival 3 years after switching was 92.7% (SD 0.81) for the tamoxifen group and 95.8% (0.65) for the group switched to anastrozole, corresponding to an absolute benefit at 3 years of 3.1% (figure 2).

Figure 3 shows the risk of recurrence of cancer stratified by nodal status, tumour grading, age, and receptor status. Although the 95% CIs of the subgroups overlap, and so the differences are not significant, the data suggest that women with G1, G2, and Gx lobular tumours responded better to anastrozole than to tamoxifen than did those with G3 tumours. For all patients, irrespective of tumour grading, the advantage of switching to anastrozole over continuing with tamoxifen was not affected by nodal status, age at surgery, or receptor positivity, although there is a (non-significant) suggestion that the benefit of anastrozole in oestrogen-receptor positive, progesterone-receptor negative patients is greater (figure 3).

	Tamoxifen	Anastrozole	Total
Total number of events	110 (2)	67 (2)	177 (4)
Locoregional events	24 (0)	20 (3)	44 (3)
Distant metastasis events	75 (4)	46 (7)	121 (11)
Contralateral events	16 (0)	12 (0)	28 (0)
Deaths			
Breast cancer-related	31	24	55
Non breast cancer-related	28	21	49

Number of patients who had had a previous event of a different type is given in parentheses.

Table 2: Recurrences and deaths by treatment group

	Tamoxifen (n=1597)	Anastrozole (n=1602)	OR (95% CI), p
Myocardial infarction	2 (<1%)	3 (<1%)	1.50 (0.17–17.9), 1.0
Embolism	9 (<1%)	2 (<1%)	0.22 (0.02–1.07), 0.064
Thromboses	12 (<1%)	3 (<1%)	0.25 (0.04–0.92), 0.034
Fractures	16 (1%)	34 (2%)	2.14 (1.14–4.17), 0.015
Endometrial cancer	7 (<1%)	1 (<1%)	1.14 (0.003–1.11), 0.069

Data are number (%) unless otherwise indicated.

Table 3: Serious adverse events by treatment group

In women in whom disease progressed, distant metastases accounted for 62% ($n=110$) of recurrences (figure 4). Metastases arose in 3% of anastrozole-treated patients and in 5% of patients treated only with tamoxifen (HR 0.61, 0.42–0.87, $p=0.0067$), indicating a 39% decrease in risk of metastases for women switching to anastrozole. When looking at distant metastases as first events only, the univariate model gives an HR of 0.54 (0.37–0.80, $p=0.0016$). Contralateral or ipsilateral recurrence accounted for only 16% ($n=28$) and 23% ($n=41$) of recurrences, respectively. More recurrences were observed in the tamoxifen group than in the anastrozole group (table 2). 59 individuals in the tamoxifen group and 45 in the anastrozole group died (table 2).

Overall survival at 3 years post-switch was slightly higher in patients who switched to anastrozole (97%) than in those who continued on tamoxifen (96%), though this difference was not significant ($p=0.16$; table 2).

Table 3 shows the incidence of serious adverse events by treatment group. There were significantly more fractures ($p=0.015$) and significantly fewer thromboses ($p=0.034$) in patients treated with anastrozole than in those treated with tamoxifen. There was also a trend towards fewer emboli ($p=0.064$) and endometrial cancers ($p=0.069$) in patients treated with anastrozole. The incidence of predefined adverse events in ABCSG trial 8 is shown in table 4. No adverse events were prespecified in the study protocol of ARNO 95. There were significantly more reports of nausea ($p=0.0162$) and a trend towards more reports of bone pain ($p=0.0546$) in the anastrozole group than in the tamoxifen group.

	Tamoxifen (n=1117)	Anastrozole (n=1120)	OR (95% CI), p
Hot flushes	560 (50%)	537 (48%)	0.92 (0.77–1.09), 0.3209
Asthenia, somnolence	29 (3%)	37 (3%)	1.28 (0.76–2.18), 0.3880
Allergy, cutaneous toxicity, skin rash	16 (1%)	26 (2%)	1.63 (0.84–3.28), 0.1628
Hair loss	24 (2%)	35 (3%)	1.47 (0.84–2.60), 0.1901
Diarrhoea	9 (<1%)	15 (1%)	1.67 (0.68–4.35), 0.3080
Nausea	10 (<1%)	25 (2%)	2.53 (1.17–5.92), 0.0162
Vaginal bleeding/discharge	195 (17%)	198 (18%)	1.02 (0.81–1.27), 0.9348
Bone pain	177 (16%)	213 (19%)	1.25 (1.00–1.56), 0.0546

Data are number (%) unless otherwise indicated.

Table 4: Predefined adverse events by treatment group in ABCSG trial 8

Discussion

Our data show that, in postmenopausal women with early breast cancer, switching to anastrozole after 2 years' tamoxifen treatment results in reduced rates of disease recurrence, particularly with respect to distant metastases. There are two possible explanations for this finding: tamoxifen resistance might be overcome by a change in treatment; or aromatase inhibitors might simply be a better treatment option, since they reduce peripheral oestrogen concentrations to extremely low levels, whereas tamoxifen is a partial agonist.

The number of women in the combined analysis who had G3 tumours was small, yet nearly a third of recurrences arose in this group. Overall, patients with G1, G2, or Gx lobular tumours responded better to adjuvant therapy than did those with G3 tumours, as expected. Undifferentiated tumours generally have a less pronounced response to endocrine therapy and could, therefore, be expected to progress more readily; the 5-year survival rate of patients with undifferentiated tumours at diagnosis is about 20% lower than that of patients with highly-differentiated or moderately-differentiated tumours.²⁵ In recognition of this difference in response, patients with undifferentiated tumours would be less likely to receive adjuvant endocrine treatment alone.

Since ABCSG trial 8 and ARNO 95 enrolled populations with a good prognosis (about three-quarters of patients were node-negative and a similar proportion received breast conservation surgery), we did not expect to see a survival difference at this stage. Furthermore, longer follow-up is needed to show a significant difference in overall survival in a trial between two active treatments than in a trial of an active treatment versus placebo.

The contrasting safety profiles of anastrozole and tamoxifen are well known. We noted significantly more fractures and significantly fewer thromboses in patients treated with anastrozole than in those who received only tamoxifen. However, we also noted a non-significant tendency towards fewer emboli and endometrial cancers in women on anastrozole. The ATAC trial¹⁵ has already provided evidence of the long-term safety and tolerability of anastrozole treatment, and no new safety concerns arose during this analysis. As expected, the fracture rate in the group switched to anastrozole was higher than in the group who received continuous tamoxifen. However, the fracture rate in the anastrozole group was lower than that seen at a similar point in the anastrozole group of the ATAC trial.²⁶ This finding could suggest a continued protective effect of tamoxifen on bone in the ABCSG trial 8/ARNO 95 patients; anastrozole-treated patients in the ATAC trial had received no previous treatment with tamoxifen. However, data from another aromatase inhibitor, exemestane, do not support this hypothesis, since patients switched to exemestane after 2–3 years'

tamoxifen¹⁷ were more likely than patients who continued on tamoxifen to have arthralgia and osteoporosis at a follow-up of 30.6 months. Results from a bone substudy of that trial showed that after 1 year, exemestane was associated with significantly greater reductions in the lumbar spine and total hip bone-mineral density (BMD) than tamoxifen. The decrease in BMD was rapid—within 6 months of switching to exemestane—and by the end of the first year, the BMD loss was similar to that seen with other aromatase inhibitors.²⁷

In a placebo-controlled trial²⁸ of the effect of exemestane on BMD in postmenopausal women with early breast cancer, the aromatase inhibitor modestly increased bone loss from the femoral neck. Management of the increased risk of fractures caused by BMD loss includes regular BMD screening. For patients with concomitant risk factors for developing osteoporosis—eg, advanced age, smoking status, family history, and high body-mass index—the administration of bisphosphonates could be considered as a prophylactic measure.

Overall, the published work indicates that there are potential benefits to switching from tamoxifen to an aromatase inhibitor after 2 years, and that patients could benefit from the antitumour effects of tamoxifen in the short term while avoiding the complications of long-term tamoxifen therapy. However, to date, the studies have been structured such that the analyses relate only to the period of switched treatment. Patients in whom cancer recurs at an early stage or who do not survive to the end of the initial tamoxifen phase are, therefore, excluded, and the randomised population is selected from patients with tumours that show a good response to endocrine therapy. As such, the results of this investigation and other switching trials apply only to those women who have successfully completed 2–3 years' adjuvant therapy for early breast cancer. They are not applicable to newly diagnosed patients, and should not be used to support a treatment strategy of starting with tamoxifen with the intention of changing to an aromatase inhibitor after 2 or more years. Overall, however, the results of these studies show the efficacy advantages attached to treatment with an aromatase inhibitor, despite the qualitative differences cross-trial comparisons reveal as to the magnitude of such advantages, definitions of predefined adverse events, or demography of patients.

The benefits of reduced recurrence of cancer when switching adjuvant therapy to an aromatase inhibitor before progression on tamoxifen might be related to cellular changes within the tumour in response to tamoxifen treatment. The effect of switching from one endocrine treatment to another after less than 2 years needs further investigation, as does switching from primary therapy with an aromatase inhibitor to other treatment modalities. Although even less thoroughly

understood than tamoxifen resistance, resistance to aromatase inhibitors over 5 years of exposure also leads to the recurrence of the original disease.²⁹

Switching treatment to an aromatase inhibitor offers the opportunity to continue adjuvant therapy for longer than 5 years, since problems of tolerability that arise from the partial agonist effects of tamoxifen are circumvented. In one study,³⁰ extended adjuvant therapy with letrozole, another non-steroidal aromatase inhibitor, conferred a significant benefit in terms of disease-free survival after 5 years' tamoxifen therapy. The extended adjuvant approach is also being investigated with 3 years' anastrozole therapy (compared with no treatment) after the standard 5 years' treatment with tamoxifen in ABCSG trial 6A.³¹

Research indicates that 5 years of treatment with tamoxifen is no longer the optimum therapy for postmenopausal women with endocrine-responsive early breast cancer. The results of the ATAC trial¹⁵ show that 5 years of anastrozole as initial endocrine therapy is better than tamoxifen for adjuvant monotherapy, and several trials support changing adjuvant therapy to an aromatase inhibitor after initial treatment with tamoxifen. Both of these findings are taken into account in the ASCO technology assessment.¹⁸ Although further investigation of the use of aromatase inhibitors is necessary to ascertain the ideal sequence and duration of adjuvant endocrine therapy, this combined analysis confirms that postmenopausal women who receive tamoxifen as adjuvant therapy should be switched to anastrozole after 2 years of treatment.

Contributors

R Jakesz is the principal investigator and chairs the writing and steering committees. W Jonat, M Gnant, and M Kaufmann participated in the coordination of the trial and the preparation of trial results for analysis. M Mittlboeck was responsible for the statistical analysis and participated in trial design. All authors contributed to the design of the study, participated in the overall operational management of the trial, contributed to data interpretation, and participated in the writing of this report.

ABCSG trial 8/ARNO 95 trial writing committee

Prof R Jakesz (chairman of the ABCSG trial 8/ARNO 95 trial steering committee, Vienna Medical University, Vienna, Austria); Prof W Jonat (member of the ABCSG trial 8/ARNO 95 trial steering committee, University Clinic Schleswig-Holstein, Kiel, Germany); Prof M Gnant (member of the ABCSG trial 8/ARNO 95 trial steering committee, Vienna Medical University, Vienna, Austria); Prof M Mittlboeck (statistician, Vienna Medical University, Vienna, Austria); Prof R Greil (Paracelsus Medical University, Salzburg, Austria); C Tausch (Linz, Austria); Prof J Hilfrich (Henriettenstiftung, Hannover, Germany); W Kwasny (Wiener Neustadt Hospital, Wiener Neustadt, Austria); Prof C Menzel (Salzburg Hospital, Salzburg, Austria); Prof H Samonigg (Graz Medical University, Graz, Austria); Prof M Seifert (Vienna Medical University, Vienna, Austria); Prof G Gademann (University of Magdeburg, Magdeburg, Germany); Prof M Kaufmann (member of the ABCSG trial 8/ARNO 95 trial steering committee); Johann Wolfgang (Goethe University, Frankfurt, Germany).

ABCSG trial 8 investigators (all institutes are in Austria)

H Aigner (Krankenhaus Spittal/Drau); P Balcke (Krankenhaus St Poelten); C Bosse (Krankenhaus Klosterneuburg); F Burger (Krankenhaus Horn); C Dadak (Medizinische Universitaet Wien); E Forsthuber (Landeskrankenhaus Klagenfurt); M Fridrik (Allgemeines

Krankenhaus Linz); R Fuegger (Krankenhaus der Elisabethinen Linz); B Gebhard (Landeskrankenhaus Voecklabruck); O Grabner (Landeskrankenhaus Rottenmann); C Groeger (Krankenhaus Neunkirchen); H Haberfellner (Landeskrankenhaus Schaefering); A Haid (Landeskrankenhaus Feldkirch); K Haider (Krankenhaus Wiener Neustadt); B Hartmann (Krankenhaus Neunkirchen); H Hausmaninger (St Johannes Spital Salzburg); CC Hinterbuchinger (Landeskrankenhaus Kirchdorf); F Hofbauer (Krankenhaus Oberpullendorf); H Hofmann (Landeskrankenhaus Feldbach); W Horvath (Krankenhaus Guessing); J Karner (Kaiser Franz Josefs Spital Wien); C W Kopf (Krankenhaus der Barmherzigen Brueder Linz); A Kretschmer (Krankenhaus Waidhofen/Thaya); E Kubista (Medizinische Universitaet Wien); R Lenzhofer (Krankenhaus Schwarzach); MG Lilgenau (Krankenanstalt Sanatorium Hera Wien); G Loncsar (Krankenhaus Hainburg); H P Ludwig (Wilhelminenspital Wien); G Luschin-Ebengreuth (Medizinische Universitaet Graz); K Mach (Krankenhaus Oberwart); P Magg (Krankenhaus Scheibbs); C Marth (Medizinische Universitaet Innsbruck); E Melbinger (Landeskrankenhaus Wolfsberg); E Nessler (Krankenhaus Dornbirn); W Neunteufel (Krankenhaus Dornbirn); R Obwegeser (Medizinische Universitaet Wien); D Pacher (Privatklinik Villach); W Passath (Landeskrankenhaus Hartberg); S Poestlberger (Krankenhaus der Barmherzigen Schwestern Linz); F Pressl (Landeskrankenhaus Steyr); R Punzengruber (Krankenhaus Amstetten); H Rabl (Landeskrankenhaus Leoben); G Ralph (Landeskrankenhaus Bruck/Mur); A C Reichenauer (Krankenhaus der Barmherzigen Brueder St Veit); G Reiner (Krankenhaus Mistelbach); K Renner (Sozialmedizinisches Zentrum Ost Wien); M Resinger (Krankenhaus der Barmherzigen Brueder Eisenstadt); P Riss (Thermenklinikum Moedling); M Rottmann (Krankenanstalt Rudolfstiftung Wien); G Salem (Krankenhaus St Poelten); H Salzer (Wilhelminenspital Wien); P Sandbichler (Krankenhaus St. Vinzenz Zams); R Schildberger (Landeskrankenhaus Freistadt); M Schmid (Medizinische Universitaet Graz); J Schueller (Krankenanstalt Rudolfstiftung Wien); H Seewann (Landeskrankenhaus Fuerstenfeld); P Sevelda (Krankenhaus Lainz Wien); B Spechtenhauser (Bezirkskrankenhaus Kufstein); G Steger (Medizinische Universitaet Wien); S Stengl (Krankenhaus der Barmherzigen Brueder Wien); H Stephan (Landeskrankenhaus Bregenz); M Stierer (Hanusch Krankenhaus Wien); S Taucher (Medizinische Universitaet Wien); J Thaler (Krankenhaus der Barmherzigen Schwestern Wels); K Toegel (Krankenhaus Krems); H Trapl (Krankenhaus Baden); K Unterrieder (Landeskrankenhaus Villach); A Urbana (Landeskrankenhaus Klagenfurt); S A Wenzl-Eybl (Krankenhaus der Barmherzigen Schwestern Ried); V Wette (Krankenhaus der Barmherzigen Brueder St. Veit); B Zeh (Donauklinikum Tulln); and W Zeilmann (Kardinal Schwarzenberg'sches Krankenhaus Schwarzach).

GABG (ARNO 95) investigators (all institutes are in Germany)

A K Bergmann (Universitaetsklinikum Tuebingen); F von Bismarck (Klinikum Rechts der Isar, Muenchen); K Brunner (Klinik fuer Senologie und Plastische Chirurgie Osnabrueck); M Butterwegge (Marienhospital Osnabrueck); O Camara (Universitaetsklinik Jena); M Carstensen (Albertinen Krankenhaus Hamburg); K Christl (Krankenhaus Eggenfelden); M H R Eichbaum (Universitaetsklinikum Heidelberg); J Feltz-Suessenbach (Klinikum Schaumburg, Stadthagen); R Fricker (Stadtkrankenhaus Hanau); M Friedrich (Universitaetsklinik Schleswig Holstein, Campus Luebeck); L Funk (St. Vincentius Krankenhaus Karlsruhe); E Goepel (Gynaekologische Gemeinschaftspraxis Hamburg); S Graeber (Universitaet Halle); C A Hanusch (Frauenklinik vom Roten Kreuz Muenchen); L Heilmann (Stadtkrankenhaus Ruesselsheim); VJ Heilmann (Universitaetsklinik Ulm); T Hitschold (Stadtkrankenhaus Worms); A Hoenig (Universitaetsklinik Wuerzburg); M Holbeck (Martin Luther Krankenhaus Schleswig); G Hopf (Elisabeth Krankenhaus Kassel); T Horvath (Kreisklinik Albstadt); H Jank (DRK Kliniken Westend Berlin); M Johnscher (Bonifatius Hospital Lingen); G Kaltenecker (Staedtisches Klinikum Karlsruhe); C Karg (Kreiskrankenhaus Waiblingen); T Liersch (Universitaetsklinik Goettingen); E Lindenlauf (Jung Stilling Krankenhaus Siegen); B Lisboa (Universitaetsklinikum Eppendorf Hamburg); K Luermann (Klinikum Hoyerswerda); I Maier (Klinikum Rosenheim); G von Minckwitz (Universitaetsklinik Frankfurt); B Mueller (Klinikum der Stadt Mannheim); C Mundhenke

(Universitaetsklinik Schleswig Holstein, Campus Kiel); A Neff (Clemenshospital Muenster); T Reimer (Universitaetsklinik Rostock); K Rensing (Universitaetsklinik Muenster); I Schrader (Henriettenstiftung Hannover); D Schulze (St Vincenz Krankenhaus Paderborn); I Schulz-Im-Busch (St. Josephs Hospital Cloppenburg); K W Schweppe (Ammerland Klinik Westerstede); G Sergius (St Joseph Krankenhaus Berlin); H K Sommer (Kreiskrankenhaus Neustadt); K Stahl (Prosper Hospital Recklinghausen); S Stein (Staedtische Krankenanstalten Idar-Oberstein); J Steller (Helios Research Center Titisee-Neustadt); E Stickeler (Universitaetsklinik Freiburg); R Stiglmayr (Siloah Krankenhaus Pforzheim); W Wiest (St Vincenz und St Elisabeth Hospital Mainz); K J Winzer (Universitaetsklinikum Charité Berlin); H Wolf (Kreiskrankenhaus Leonberg); K Wollschlaeger (Universitaetsfrauenklinik Magdeburg); and B Zieren-Ernhardt (Universitaetsklinik Charité Berlin).

Conflict of interest statement

R Jakesz, W Jonat, and M Kaufmann have done research sponsored by AstraZeneca. M Gnant, M Mittlboeck, R Greil, C Tausch, J Hilfrich, W Kwasny, C Menzel, H Samonigg, M Seifert, and G Gademann declare that they have no conflict of interest.

Acknowledgments

We thank all patients in Austria and Germany for participating in this investigation, the ABCSG and GABG trialists, the staff at the Vienna and Frankfurt trial offices, the respective study site affiliates, and Wolfgang Draxler and Karl Thomanek for editorial and biometrical expertise. We also thank AstraZeneca for making the study medication available and Complete Medical Communications for editorial assistance (funded by AstraZeneca).

References

- 1 Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. IARC CancerBase, version 2.0. Lyon: IARC Press, 2004. http://www-depdb.iarc.fr/globocan/table2_sel.htm (accessed July, 2005).
- 2 Anderson WF, Chatterjee N, Ershler WB, Brawley OW. Estrogen receptor breast cancer phenotypes in the surveillance, epidemiology, and end results database. *Breast Cancer Res Treat* 2002; **76**: 27–36.
- 3 Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. *J Clin Oncol* 2003; **21**: 3357–65.
- 4 Peto R. Five years of tamoxifen: or more? *J Natl Cancer Inst* 1996; **88**: 1791–93.
- 5 Fisher B, Dignam J, Bryant J, et al. Five versus more than five years of tamoxifen therapy for breast cancer patients with negative lymph nodes and estrogen receptor-positive tumors. *J Natl Cancer Inst* 1996; **88**: 1529–42.
- 6 Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **365**: 1687–717.
- 7 Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994; **86**: 527–37.
- 8 Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN. Use of tamoxifen for breast cancer: twenty-eight years later. *J Clin Oncol* 1995; **13**: 513–29.
- 9 Clarke R, Leonessa F, Welch JN, Skaar TC. Cellular and molecular pharmacology of antiestrogen action and resistance. *Pharmacol Rev* 2001; **53**: 25–71.
- 10 Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer. (Cochrane Review). In: The Cochrane Library, Issue 1. Chichester: John Wiley & Sons, 2004.
- 11 Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol* 1996; **14**: 2738–46.
- 12 Morandi P, Middleton LP, Mirza NQ, et al. Occult breast cancer (OBC), a retrospective analysis of clinico-pathological characteristics and long-term outcome: the University of Texas MD Anderson Cancer Center experience. *Breast Cancer Res Treat* 2004; **88**: S165 (abstract).
- 13 Geisler J, King N, Anker G, et al. In vivo inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. *Clin Cancer Res* 1998; **4**: 2089–93.
- 14 Geisler J, Haynes B, Anker G, Dowsett M, Lønning PE. Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. *J Clin Oncol* 2002; **20**: 751–57.
- 15 The ATAC Trialists' Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005; **365**: 60–62.
- 16 Boccardo F, Rubagotti A, Puntoni M, et al. Switching to anastrozole versus continued tamoxifen treatment of early breast cancer: preliminary results of the Italian Tamoxifen Anastrozole (ITA) trial. *J Clin Oncol* 2005; published online July 11, DOI: 10.1200/JCO.2005.04.120.
- 17 Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004; **350**: 1081–92.
- 18 Winer EP, Hudis C, Burstein HJ, et al. American Society of Clinical Oncology technology assessment on the use of aromatase inhibitors as adjuvant therapy for postmenopausal women with hormone receptor-positive breast cancer: status report 2004. *J Clin Oncol* 2005; **23**: 619–29.
- 19 Bloom HJ, Richardson WW. Histological grading and prognosis in breast cancer: a study of 1409 cases of which 359 have been followed for 15 years. *Br J Cancer* 1957; **11**: 359–77.
- 20 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31**: 103–15.
- 21 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–81.
- 22 Peto R, Peto J. Asymptotically efficient rank invariant procedures. *J R Stat Soc* 1972; **135**: 185–207.
- 23 Mantel N. Evaluation of survival data and two new rank order statistics arising in its consideration. *Cancer Chemother Rep* 1966; **50**: 163–70.
- 24 Cox DR. Regression models and life tables. *J R Stat Soc* 1972; **34**: 187–220.
- 25 Lundin J, Lundin M, Holli K, et al. Omission of histologic grading from clinical decision making may result in overuse of adjuvant therapies in breast cancer: results from a nationwide study. *J Clin Oncol* 2001; **19**: 28–36.
- 26 The ATAC Trialists' Group. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002; **359**: 2131–39.
- 27 Coleman RE, Banks LM, Hall E, et al. Intergroup exemestane study: 1 year results of the bone sub-protocol. *Breast Cancer Res Treat* 2005; **88**: S35 (abstract).
- 28 Lønning PE, Geisler J, Krag LE, et al. Effects of exemestane administered for 2 years versus placebo on bone mineral density, bone biomarkers, and plasma lipids in patients with surgically resected early breast cancer. *J Clin Oncol* 2005; published online June 27, DOI: 10.1200/JCO.2005.07.097.
- 29 Goss P. Anti-aromatase agents in the treatment and prevention of breast cancer. *Cancer Control* 2002; **9** (2 suppl): 2–8.
- 30 Goss PE, Ingle JN, Martino S, et al. A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early-stage breast cancer. *N Engl J Med* 2003; **349**: 1793–802.
- 31 Jakesz R, Samonigg H, Greil R, et al. Extended adjuvant treatment with anastrozole: results from the Austrian Breast and Colorectal Cancer Study Group Trial 6a (ABCSG-6a). *Proc Am Soc Clin Oncol* 2005; **23**: 10s (abstract).