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Tamoxifen and Anastrozole As a Sequencing Strategy: A Randomized Controlled Trial in Postmenopausal Patients With Endocrine-Responsive Early Breast Cancer From the Austrian Breast and Colorectal Cancer Study Group

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ABSTRACT

Purpose
Anastrozole (ANA) alone delivers significant disease-free survival benefits over tamoxifen (TAM) monotherapy in postmenopausal women with early estrogen receptor–positive breast cancer. The ABCSG-8 (Austrian Breast and Colorectal Cancer Study Group 8) study is a large phase III clinical trial addressing the sequence strategy containing ANA in comparison with 5 years of TAM in a low- to intermediate-risk group of postmenopausal patients.

Patients and Methods
Endocrine receptor–positive patients with G1 or G2 tumors were eligible. After surgery, patients were randomly assigned to 5 years of TAM or 2 years of TAM followed by 3 years of ANA. Adjuvant chemotherapy and G3 and T4 tumors were exclusion criteria. Intention-to-treat and censored analyses of on-treatment recurrence-free survival (RFS) were performed, and exploratory survival end points and toxicity were investigated.

Results
Information from 3,714 patients, including 17,563 woman-years, with a median of 60 months of follow-up was available for this analysis. Median age was 63.8 years, 75% were node negative, and 75% had T1 tumors. Sequencing of ANA after identical 2-year treatment with TAM in both arms did not result in a statistically significant improvement of RFS (hazard ratio [HR], 0.80; 95% CI, 0.63 to 1.01; $P = .06$). Exploratory analyses of distant relapse-free survival indicated a 22% improvement (HR, 0.78; 95% CI, 0.60 to 1.00). On-treatment adverse events and serious adverse events were consistent with known toxicity profiles of ANA and TAM treatment.

Conclusion
Despite a low overall rate of recurrence in a population with breast cancer at limited risk of relapse, the a priori sequence strategy of 2 years of TAM followed by 3 years of ANA led to small outcome and toxicity benefits.

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INTRODUCTION

The antiestrogen tamoxifen (TAM) has been the established adjuvant endocrine therapy for postmenopausal women with early breast cancer for close to 30 years.[1] To investigate a potentially superior benefit of estrogen depletion with aromatase inhibitors, large clinical trials have previously presented detailed analyses. The ATAC (Arimidex, Tamoxifen, Alone or in Combination)[2] and BIG 1-98 (Breast International Group 1-98)[3] trials have explored the comparison of TAM monotherapy with the upfront use of aromatase inhibitors (AIs). A recent meta-analysis of these two trials reported a 23% proportional reduction in recurrences with an absolute 3.9% gain at 8 years after starting endocrine treatment.[4]

Other trial designs have demonstrated that switching to an additional 3 years of AIs after an initial 2- to 3-year treatment with TAM results in similar benefits concerning disease recurrence; some of these trials and meta-analyses of the data have even suggested significant improvements in overall survival (OS) in comparison with 5 years of

TAM monotherapy.[4-7] Among these results, data from 2,262 women randomly assigned in the ABCSG-8 (Austrian Breast and Colorectal Cancer Study Group 8) trial have been reported in a combined analysis with ARNO95 (Arimidex, Nolvadex 95).[8]

These so-called switching trials and analyses randomly assign and observe patients at the time of potential switch and avoid selective treatment crossover resulting from earlier random assignment at diagnosis. This early random assignment, as in our trial and that of Mouridsen et al,[3] allows unbiased estimation of survival starting at diagnosis but must address substantial bias from women receiving unintended treatment.

To address the question of survival after an endocrine sequence treatment (as opposed to efficacy of switch from TAM to AI), BIG 1-98 compared both monotherapies with two possibilities of sequential endocrine treatment (letrozole followed by TAM and vice versa [four-group option]). The efficacy analyses showed that sequential treatments were not superior to 5 years of letrozole; the average outcomes of a sequence therapy versus letrozole alone did not suggest statistically relevant differences in either direction. This was corroborated by the results of the TEAM (Tamoxifen Exemestane Adjuvant Multinational) trial.[9]

With respect to patients with favorable prognostic factors, the absolute benefit of AI therapy is less established. For example, in the node-negative subgroup of BIG 1-98, neither 5 years of letrozole nor a sequence of letrozole was established to have a significant efficacy advantage over 5 years of TAM. Furthermore, prospective data specifically investigating patients with low- to intermediate-risk treated in the absence of chemotherapeutic agents are scarce. In the Western world, this subgroup accounts for almost 50% of the population with early breast cancer. It is precisely this group of women for whom, with respect to long-term outcome, it is unclear whether optimal use of an AI is up front or after 2 or even 5 years of TAM. Currently, the safety of withholding an AI for 2 to 5 years should be evaluated in light of the on-treatment toxicity and incidence of breast cancer recurrences and deaths.

Here we report the 5-year outcome analysis of ABCSG-8, a prospective evaluation of a well-defined low- to moderate-risk group of endocrine responsive, postmenopausal patients with breast cancer not receiving any other systemic therapy. Both groups of patients were treated with an initial 2 years of TAM and sequenced to anastrozole (ANA) versus TAM for an additional 3 years.

PATIENTS AND METHODS

ABCSG-8 is a prospective, multicenter, randomized, open-label study comparing 5 years of TAM treatment with 2 years of TAM followed by 3 years of ANA. Random assignment occurred immediately after surgery, and no (neo) adjuvant chemotherapy was allowed.

Patients

Patients were postmenopausal women age 80 years or younger with primary, operable, histologically verified, estrogen receptor (ER) –positive and/or progesterone receptor (PgR) –positive, grade 1 or 2 ductal and Gx lobular invasive breast cancer. Additional information concerning the definition of menopausal status, endocrine receptor assessment, surgery, radiotherapy, random assignment, stratification, study treatment, and patient follow-up has been published previously[8] and included in the Appendix (online only). Study recruitment started in January 1996 and ended in June 2004.

Adverse events (AEs) of special interest were predefined in the study protocol and recorded at each study visit. For the purpose of analysis, they were counted once per patient and described with absolute frequencies and percentages (Appendix Table A1, online only). Serious AEs (SAEs) were stored in the sponsor database and coded according to MedDRA version 12.1 (MSSO, Chantilly, VA; http://meddramsso.com). Events until 60 months are presented. Appendix Table A2 (online only) lists all SAEs on a preferred-term level for this period with either an incidence greater than 1% or a 0.05 difference in relative frequency between treatment arms or statistically significant difference between treatment arms (two-sided $P < .05$). Furthermore, slightly deviating from the MedDRA architecture, SAEs were grouped according to event types (Appendix, online only) with clinical relevance to endocrine therapy.

All relevant institutional review boards in Austria approved ABCSG-8. The study was carried out in accordance with the Declaration of Helsinki.

Statistical Analysis

Patients were allocated to treatment using the minimization method according to Pocock et al.[10] After the publication of the combined ABCSG-8/ARNO95 analysis, 348 patients (9.4%) who had been randomly assigned to 5 years of TAM selectively crossed over to the sequential treatment arm (Fig 1). In line with a similar publication, all patients selectively changing therapy arm were censored at the time of crossover.[3] These analyses have been termed censored analyses.

Starting in 2004, postmenopausal women with prior 4 to 6 years of endocrine therapy were eligible for extended adjuvant treatment with ANA according to protocol ABCSG-16 (SALSA [Secondary Adjuvant Long-Term Study With Arimidex]; NCT00295620). Although recruitment for ABCSG-16 was finalized at 3,486 patients in June 2010, that trial is still an open trial, with patients receiving active treatment at the time of this analysis; thus, event data from patients enrolled onto that trial must not be used. Another selective censorship of ABCSG-8 patients entering ABCSG-16 after ABCSG-8 would potentially lead to several additional biases. As a result, we decided to limit follow-up of all patients enrolled onto ABCSG-8 up to the time when they entered ABCSG-16 or up to 60 months.

The primary end point of this analysis was recurrence-free survival (RFS) as recently defined in the STEEP system[11] as time from random assignment to the earliest occurrence of local or distant recurrence or death as a result of any cause. Distant relapse-free survival (DRFS; including distant recurrence and death as result of any cause), disease-free survival (DFS; including new contralateral tumors, second primary cancer, local and distant recurrence, and death as result of any cause), and OS were defined exploratory end points. Analyses were performed according to the intention-to-treat (ITT) principle as well as on the basis of the censored population. Median follow-up was calculated by inverse Kaplan-Meier method.

Data are graphically depicted using Kaplan-Meier curves and were tested by log-rank tests. Hazard ratios (HRs) and their corresponding 95% CIs were estimated by Cox proportional hazards regression. Additionally, multivariate Cox regressions were performed using the primary end point of RFS in the censored population to evaluate treatment effect adjusted for known prognostic factors such as nodal status, age, hormone receptor expression, and tumor stage. Interaction between treatment and prognostic factors were tested using RFS in the censored population, adjusting for remaining prognostic factors. Toxicity evaluation is included in the Appendix, (online only). All analyses were calculated using SAS version 9.1 (SAS Institute, Cary, NC).

Role of the Funding Source

The study protocol was developed and written by R.J. and M.G. The trial was managed by ABCSG. Funding and organizational support was provided by the trial sponsor AstraZeneca. ABCSG statisticians and investigators carried out all data analyses independent of the sponsor.

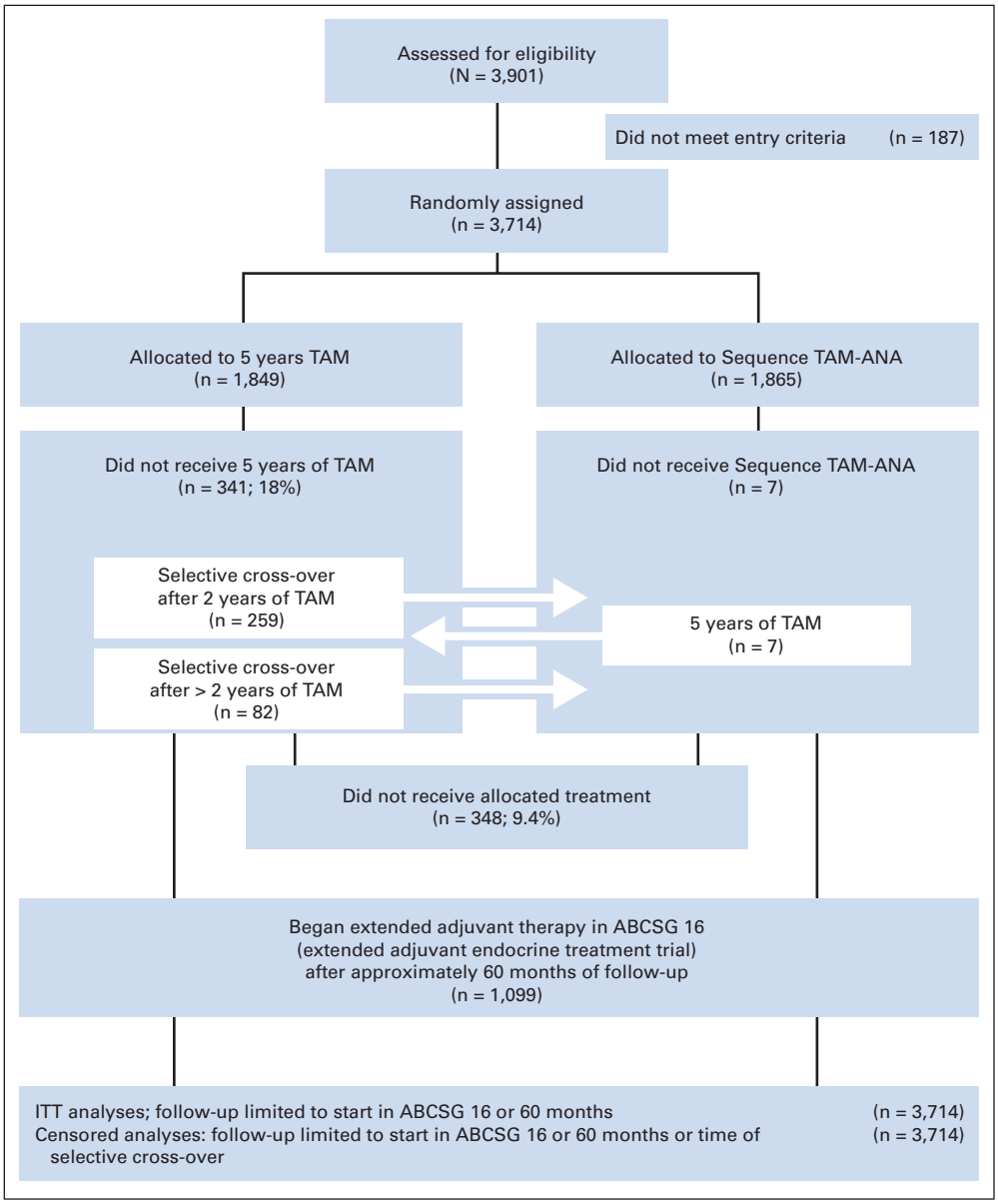

Fig 1. CONSORT diagram. ABCSG, Austrian Breast and Colorectal Cancer Study Group; ANA, anastrozole; ITT, intention to treat; TAM, tamoxifen.

RESULTS

Trial Profile

This trial included 3,714 postmenopausal patients for random assignment. Cohorts, treatment allocation, follow-up, and analyses are depicted in Figure 1. Data from 348 women (9.4%) were censored at the time of crossover for the censored analyses. This included 341 women (18%) from the TAM arm. All follow-up was censored at either 60 months or at the time of random assignment in ABCSG-16 for both the ITT and censored analyses. As a consequence, median follow-up in this analysis is 60 months, with a range of 0.5 to 60 months (mean follow-up: ITT analysis, 57.8 months; censored analysis, 55.5 months). Follow-up included 17,563 woman-years (8,709 in TAM arm; 8,853 in sequence arm).

Patient Characteristics

The treatment groups were well balanced in terms of all clinical and therapeutic parameters assessed (Table 1). Median age at the time of surgery was 63.8 years; 74.6% of patients were node negative, and 74.9% had tumors smaller than 2 cm. A high expression of ER (ER+++) was found in 61.9% of patients, and 58.1% showed a combined expression of ER++ and PgR++ or higher. ER-negative, PgR-positive tumors were found in 1.2% of patients (46 patients; 23 in each arm); 75.7% had G2 tumors, and 19.9% had G1. Breast conservation was achieved in 82% of patients, and 70.4% received radiotherapy.[13]

Efficacy

Women assigned to the sequence of TAM followed by ANA showed a decrease of 20.0% (ITT: HR, 0.80; 95% CI 0.63 to 1.01; $P = .06$) in risk of recurrence (124 *v* 152 events; Fig 2A). This was a

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Table 1. Patient Clinical Characteristics

Characteristic	TAM		TAM → ANA		Total	
	No.	%	No.	%	No.	%
Total	1,849		1,865		3,714	
Age at surgery, years						
Median	64.0		63.6		63.8	
Range	41.4-80		44.1-80.5		41.4-80.5	
Affected nodes						
N0	1,382	74.7	1,388	74.4	2,770	74.6
N1 (one to three)	412	22.3	419	22.5	831	22.4
N2 (four to nine)	54	2.9	58	3.1	112	3.0
Unknown	1	< 0.1	0	0.0	1	< 0.1
Tumor size						
T1	1,383	74.8	1,399	75.0	2,782	74.9
T2	450	24.3	449	24,1	899	24.2
T3	16	0.9	17	0.9	33	0.9
ER status						
Negative (−)	23	1.2	23	1.2	46	1.2
Low expression (+)	168	9.1	168	9.0	336	9.0
Medium expression (++)	531	28.7	496	26.6	1,027	27.7
High expression (+++)	1,126	60.9	1,174	62.9	2,300	61.9
Unknown	1	< 0.1	4	0.2	5	0.1
PgR status						
Negative (−)	351	19.0	333	17.9	684	18.4
Low expression (+)	341	18.4	336	18.0	677	18.2
Medium expression (++)	585	31.6	629	33.7	1,214	32.7
High expression (+++)	568	30.7	564	30.2	1,132	30.5
Unknown	4	0.2	3	0.2	7	0.2
Hormone receptor expression						
ER++/PgR++ or higher	1,062	57.44	1,097	58.9	2,159	58.1
Lower than ER++/PgR++	783	42.35	765	41.0	1,548	41.7
Unknown	4	0.2	3	0.2	7	0.2
Type of surgery						
Breast-conserving surgery	1,515	81.9	1,532	82.1	3,047	82.0
Modified radical mastectomy	334	18.1	333	17.9	667	18.0
Radiation[12]						
Yes	1,309	70.8	1,305	70.0	2,614	70.4
No	530	28.7	548	29.4	1,078	29.0
Unknown	10	0.5	12	0.6	22	0.6
Grading						
G1	363	19.6	376	20.2	739	19.9
G2	1,414	76.5	1,397	75.0	2,811	75.7
Gx lobular	72	3.9	92	4.9	164	4.4

Abbreviations: ANA, anastrozole; ER, estrogen receptor; PgR, progesterone receptor; TAM, tamoxifen.

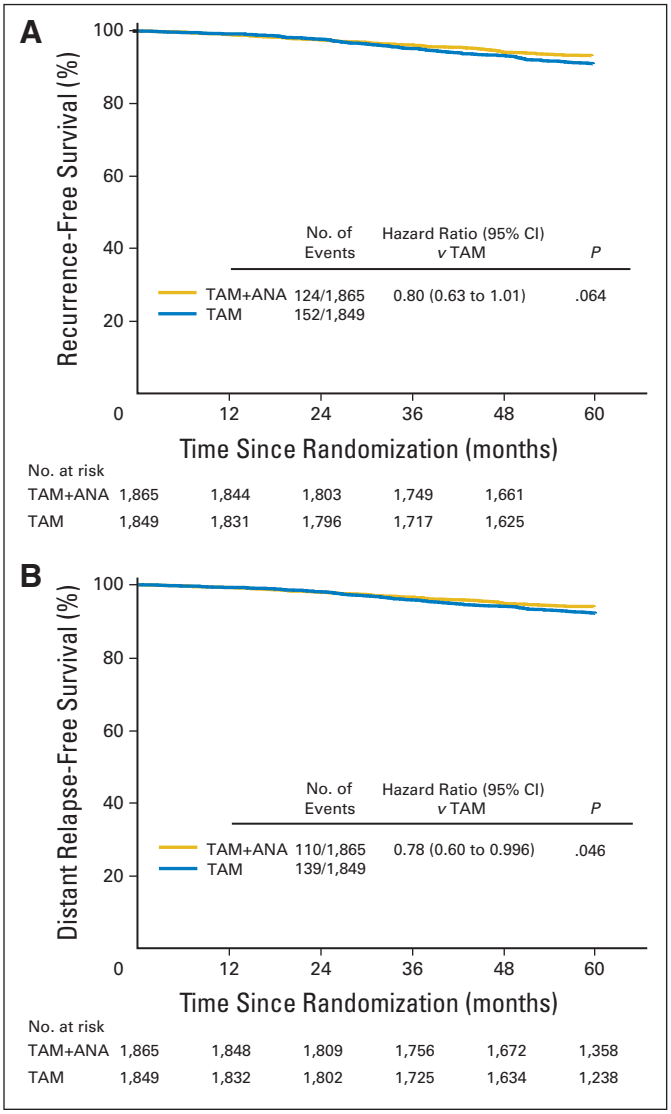

Fig 2. Intention-to-treat analyses of (A) recurrence-free survival and (B) distant relapse-free survival. ANA, anastrozole; TAM, tamoxifen.

statistically nonsignificant finding concerning the primary end point of this analysis. Compensating for selective crossover, the risk of recurrence decreased by 24% (censored analysis: HR, 0.76; 95% CI, 0.60 to 0.97).

In addition to RFS, Figure 3 depicts HRs and 95% CIs for the exploratory efficacy end points of DFS, DRFS, and OS and provides a better understanding of which types of events drive the efficacy of study arms. In addition to recurrences and deaths, the calculation of DFS included both secondary malignomas and contralateral breast cancer. ITT analysis did not indicate a benefit concerning this end point (HR, 0.91; 95% CI, 0.75 to 1.10; $P = .33$). There was no statistically significant difference between study arms concerning overall survival (ITT: HR 0.87; 95% CI, 0.65 to 1.16; $P = .34$). However, the observed difference in recurrence did not seem to come from a reduction in local recurrence, because DRFS revealed a 22% reduction in risk in favor of ANA (ITT: HR, 0.78; 95% CI, 0.60 to 0.99; $P < .05$).

Both RFS and DRFS are depicted in Kaplan-Meier prevalence curves from the ITT analyses (Figs 2A, 2B). At 60 months of follow-up, 139 DRFS versus 110 DRFS events translate to an absolute difference of 1.6%. In terms of RFS, an absolute 1.6% difference in 60-month survival rates in favor of ANA has been recorded (152 *v* 124 events).

A descriptive analysis of all first events (ITT analysis) is provided in Table 2. There was a low rate of locoregional (n = 36) and contralateral (n = 29) recurrences, with no difference between treatment arms. Distant recurrences and secondary malignant conditions each accounted for approximately one third of all first events, and deaths without previous recurrence comprised 21.3% of all events. There were fewer distant recurrences in the ANA arm (n = 72 *v* n = 57) and fewer deaths recorded for the sequence strategy; 49.2% (n = 87) of all deaths were recorded without prior recurrence of breast cancer; 47 of these deaths occurred in the TAM arm, and 39 occurred in the ANA arm.

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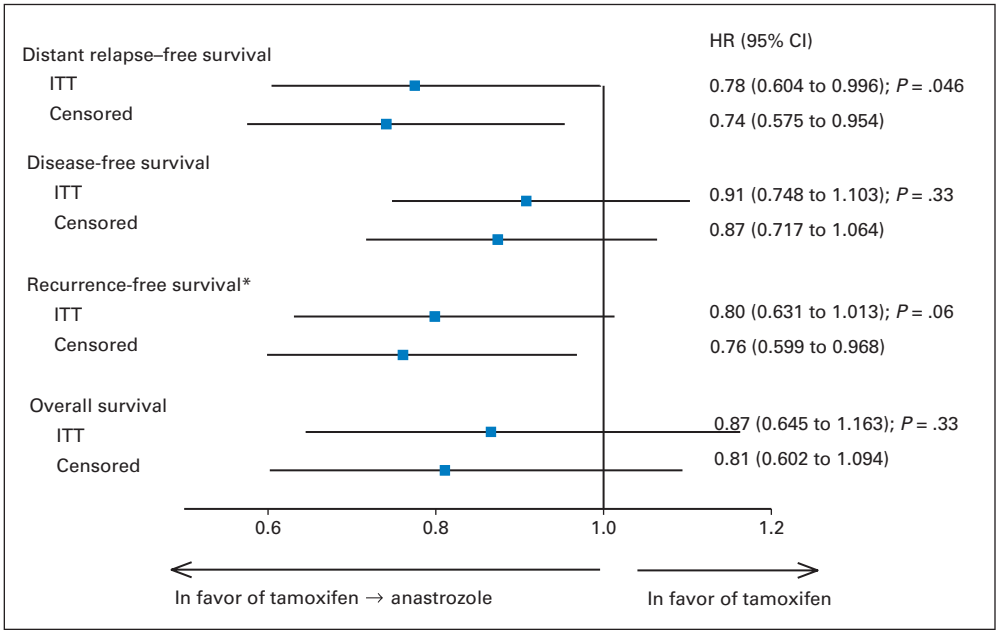

Fig 3. Efficacy summary. (*) Recurrence-free survival equal to disease-free survival without contralateral breast cancer and without secondary malignoma. HR, hazard ratio; ITT, intention to treat.

In summary, at 60 months of follow-up, the group difference of the RFS primary end point did not reach statistical significance. However, exploratory analyses of distant metastases indicated a clinically meaningful benefit concerning the anticancer efficacy of the sequence strategy.

Multivariate Analyses and HRs in Subgroups

To further explore the effect of sequential ANA treatment on the risk of recurrence, treatment was evaluated in combination with known prognostic factors (Table 3). Clearly, age older than 60 years, positive nodal status, and increasing tumor size were demonstrated to increase risk of recurrence. High expression of both ER and PgR decreased risk of recurrence by 20% in multivariate analysis. Finally, treatment with ANA was associated with a significant 22% decrease in risk. There were no significant interactions between any of the covariates and the type of treatment allocated. The treatment effect of TAM followed by ANA was similar in subgroups determined by baseline characteristics of the study population (Appendix Fig A1, online only).

Safety and Toxicity

Approximately 70% of all patients experienced hot flushes, and one third of patients suffered from vaginal bleeding or discharge at least once during the study period. Both of these AEs were equally distributed. There was a moderate, statistically significant difference with 29.3% of patients experiencing bone pain in the TAM arm versus 32.9% in the sequence arm ($P < .02$). There were no differences concerning asthenia, hair loss, allergy/skin toxicity, nausea, and diarrhea between treatment arms (Appendix Table A1, online only).

Selected MedRA databank–coded SAE preferred terms are listed in Appendix Table A2 (online only). Furthermore, SAEs were grouped according to categories frequently associated with antihormonal treatment (Appendix Table A3, online only). Fracture was a rare event,

Table 2. First Events (ITT analysis)

Event	TAM		TAM → ANA		Total	
	No. of Events	No. of Patients With Simultaneous Event	No. of Events	No. of Patients With Simultaneous Event	No. of Events	No. of Patients With Simultaneous Event
All first events	212		196		408	408
Locoregional recurrence	18	3	18	3	36	6
Distant recurrence	72	6	57	3	129	9
Contralateral breast cancer	14		15		29	
Secondary malignoma	67	3	70		137	3
Death						
All	94		83		177	
Without previous recurrence	47		39		87	

NOTE. Events occurring simultaneously are recorded twice.
Abbreviations: ANA, anastrozole; ITT, intention to treat; TAM, tamoxifen.

Table 3. Multivariate Cox Regression Analysis (censored data)

Covariate	HR	95% CI	*P*
Therapy arm			
TAM → *v* TAM	0.78	0.61 to 0.99	.0407
Nodal status			
Negative *v* positive	1.88	1.47 to 2.41	< .001
Age, years			
≤ 60 *v* > 60	1.60	1.20 to 2.12	< .0013
HR expression			
High *v* low*	0.70	0.55 to 0.89	.0032
Tumor size			
T1 *v* T2 and T3	2.23	1.74 to 2.85	< .001

NOTE. End point: recurrence-free survival.
Abbreviations: ER, estrogen receptor; HR, hazard ratio; PgR, progesterone receptor.
*High hormone receptor expression refers to ER++] and PgR++ or higher.

with a moderately lower rate in the TAM arm not reaching statistical significance (1.5% *v* 2.3%; $P < .08$). By far the most common SAEs recorded were events summarized as uterine disorders (n = 636); 20.2% of women in the TAM arm experienced this type of SAE, as opposed to 14.1% in the sequence arm ($P < .001$). The vast majority of these SAEs originated from reports of uterine polyps and endometrial hyperplasia (Appendix Table A2, online only). Musculoskeletal disorders were significantly less frequent (2.8% *v* 4.1%; $P < .03$) in the TAM arm. There were no significant differences detected in SAEs grouped as cardiovascular or thromboembolic.

DISCUSSION

ABCSG-8 is a large phase III trial evaluating adjuvant endocrine therapy in the setting of postmenopausal, hormone receptor–positive early breast cancer. The aim of this study was to compare the efficacy and toxicity of an additional 3 years of ANA versus an additional 3 years of TAM, after a common 2 years of TAM treatment in both arms. To our knowledge, this trial, together with part of the four-arm option of BIG 1-98, is the only large phase III trial exploring the sequential therapy of an AI with TAM monotherapy.

A comparison of patient characteristics of ABCSG-8 with those of similar endocrine treatment trials[2,12,14,15] clearly shows a patient population with low- to intermediate-risk factors for recurrence; close to 75% of patients were node negative and had tumors smaller than 2 cm. In addition, ABCSG-8 excluded women with G3 tumors and did not allow adjuvant chemotherapy. ABCSG-8 shows the highest survival rates at 5 years of follow-up in comparison with BIG 1-98 or the ATAC trial, for example. We recorded a 5-year DFS of 89.5% in the sequence arm and 88.5% in the monotherapy arm (data not shown; DFS exploratory end point in ABCSG-8). These results confirm both the estimate of risk based on simple prognostic criteria and add to the clinical evidence indicating that these subgroups can be spared cytotoxic treatment.

The primary end point of this study shows a nonsignificant 20% reduction in recurrence risk. The small efficacy benefits observed were driven by a lower number of distant metastases and deaths. Patients were randomly assigned at diagnosis. Our study and BIG 1-98 have shown substantial treatment crossover after 2 years of TAM. Random assignment after 2 years with prospective registration at diagnosis would have prevented this study limitation.

Furthermore, because of the identical treatment with TAM for 2 years, the assumption of proportional hazards is not satisfied by definition if all 5 years are included in the analysis. An alternative analysis strategy that would have estimated treatment effects in years 3 to 5 might have shown even larger treatment effects of ANA. Despite these limitations, it seems prudent to identify locoregional and contralateral events as extremely rare events in both arms and describe the observed reduction in distant recurrences as clinically meaningful to disease control.

Are there alternative motives, other than individually occurring toxicities, to treat postmenopausal women with a TAM-ANA sequence? Women with ER-positive disease, particularly, have been shown to remain at sustained risk of relapse up to 15 years after diagnosis despite favorable prognostic factors.[16] In line with this finding, excellent efficiency has been demonstrated with extended treatment with an AI after 5 years of TAM, especially in node-positive women.[17,18] This widening of focus from early recurrence of disease to a 15- to 20-year time span of possible recurrence may provide a renewed rationale for sequences including TAM. For a postmenopausal woman diagnosed with ER-positive breast cancer, it is currently not clear whether an AI would optimally benefit her long-term survival when used up front, after 2 years of TAM, or after 5 years of TAM.[19]

Predictive factors of patients most likely to benefit from an AI, or at least the best possible definition of patient risk, are a common goal in breast cancer research. ABCSG has carried out translational work evaluating a gene expression signature. In that study,[20] we validated that the molecular predictor is able to improve the prediction of distant metastases otherwise estimated by clinicopathologic factors. Furthermore, we[21] and others[22] have investigated host-related factors such as body mass index to predict AI benefit. In addition, pharmacogenomic tools to predict the individual metabolism of TAM may be of particular interest.[23]

This study did not yield clear differences concerning AEs commonly associated with endocrine therapy. This fairly even distribution of AEs experienced should be attributed to the following: one, a spectrum of adverse effects that is largely overlapping between TAM and ANA; and two, the identical 2-year initial TAM treatment in both arms. However, the continued treatment with TAM led to a significant increase of uterine disorders reported as SAEs most likely resulting from surgical interventions such as curettage. This analysis reports on-treatment SAEs and finds a clear one-third increase in endometrial hyperplasia and polyps. To some degree, this most likely reflects the Austrian guidelines concerning the indications for curettage at the time,[24] but nevertheless, these data represent a serious concern when prescribing TAM.

In summary, ABCSG-8 provides prospective data about the sequence of TAM-ANA in comparison with 5 years of TAM therapy in a large, low- to intermediate-risk cohort treated without chemotherapy. On average, the inclusion of ANA in the first 5 years of endocrine therapy leads to small improvements in breast cancer recurrence and on-treatment toxicity. These data support the sequential use of ANA in women considered to have a favorable prognosis.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Manuscript writing: All authors
Final approval of manuscript: All authors

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Appendix

This appendix has been provided as an online supplement in order to give additional information about the ABCSG-8 (Austrian Breast and Colorectal Cancer Study Group 8) trial:

Section I

Short synopsis of ABCSG-8 protocol and amendments in English language:

Adjuvant endocrine therapy in postmenopausal patients with hormone receptor–positive breast cancer with low to intermediate grading. Adjuvant endocrine therapy with: (1) tamoxifen (TAM; Nolvadex; AstraZeneca, London, United Kingdom) for 5 years; (2) TAM for 2 years followed by anastrozol (ANA; Arimidex, AstraZeneca) for 3 years.

Eligibility. Inclusion criteria: postmenopausal (last menstruation > 1 year, if doubt follicle-stimulating hormone/luteinizing hormone in serum); primary breast cancer; estrogen receptor (ER) and/or progesterone receptor (PgR) positive; R0 resection; G1 or G2; no distant metastasis; informed consent. Exclusion criteria: premenopausal or uncertain menopausal status; any type of preoperative chemotherapy or hormone or radiation therapy; other previous or current malignoma; contraindication against TAM or ANA (including renal, hepatic failure); G3; random assignment fails to occur within fewer than 6 weeks of surgery; ductal carcinoma in situ (without invasive cancer); T4; uncertain or unknown hormone receptor status; missing/uncertain compliance; age older than 80 years; any comorbidity, including infections that may interfere with adjuvant protocol.

Stratification (original protocol). Age; pT; pN; grading; locoregional therapy; receptor status; participating center.

Planned intervention. Random assignment to 5 years of TAM versus 2 years of TAM followed by 3 years of ANA. Furthermore, a subprotocol concerning the value of radiation in patients with N0 tumor smaller than 3 cm and breast conserving therapy was carried out, as detailed previously (Potter R, Gnant M, Kwasny W, et al: Int J Radiat Oncol Biol Phys 68:334-340, 2007).

Primary and secondary end points. Original, amended for combined analysis, and current:

Original protocol (1995). The initial primary end point was overall survival (OS). In June 2004, this was changed in view of the combined analysis with ARNO95 (Arimidex, Nolvadex 95) in amendment VI.

Amended protocol. Amended for combined analysis (Jakesz R, Jonat W, Gnant M, et al: Lancet 366:455-462, 2005). Primary end point: event-free survival (locoregional, distant metastasis, contralateral breast cancer, and any death). Secondary end point: OS.

Current analysis. We have adhered to the STEEP guidelines to define end points. Recurrence-free survival was chosen as primary end point because it corresponds to the previously published event-free survival (EFS), with the exception of contralateral breast cancer (included in EFS but not recurrence-free survival). However, contralateral invasive breast cancers were rare and evenly distributed between treatment groups.

Statistical plan. Plan and history:

Original protocol. The following assumptions were made: 70% OS versus 77% in the ANA arm, power of 85%: 1,200 patients. This now historical assumption was amended in 2002: 90% versus 92.3%, to detect a hazard ratio of 1.31 with a power of 85% with a two-sided *P* value of .05. The total number of patients was increased to 3,500. An interim analysis at the significance level of .001 was planned after 66% of patients were recruited, but amendment VI became valid before the planned interim analysis was due.

Amendment VI. End point: EFS. Statistical plan for combined analysis of ABCSG-8/ARNO95: the analysis of data was to be triggered by a total of 278 events. This allowed the detection of a hazard ratio of 1.4 at a power of 80% with a two-sided *P* value of .05. Interim analyses were planned on reaching 139 and 209 events, using a significance level of .001 (stopping boundary) to maintain a significance level of .05 for the final analysis. The ABCSG/ARNO95 publication was triggered after 143 events were observed in April 2004. At this time, the stopping boundary for EFS had been reached, and the independent data monitoring committee decided in November 2004 to publish the data.

Current analysis. Decided by the ABCSG scientific advisory board. This analysis was not a preplanned per protocol analysis. This analysis does have a substantial intersection of data with the ABCSG/ARNO95 analysis. Again included in this full analysis of 3,714 patients are 2,262 patients previously analyzed (from switch but not from diagnosis). Multiplicity issues arising from this are not addressed statistically. However, several factors prompted the scientific board to analyze and publish the data: (1) at the time of the combined analysis, 1,080 women were not included, because they had not finished their initial 2 years of TAM (switch analysis); (2) few data describe the influence of sequencing aromatase inhibitors as opposed to the switch to aromatase inhibitors after prior TAM therapy; (3) this data set is unique with respect to the exclusion of G3 tumors but also concerning the distribution of other risk factors.

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The board advised the following outlines for the current analysis: to analyze the entire data set of 3,714 eligible women; to compare treatment arms using STEEP-defined end points; to describe the bias of selective crossover; to take into account the bias of extended adjuvant therapy within ABCSG-16.

Section II

Additional information concerning patients and methods. Postmenopausal status was assumed if last menstruation was at least 12 months before study entry, or when patients had undergone bilateral ovariectomy, or when follicle-stimulating hormone and luteinizing hormone concentrations were within postmenopausal ranges. All patients had ER- or PgR-positive disease. Hormone receptor expression was scored as previously described (Reiner A, Neumeister B, Spona J et al: Cancer Res 50:7057-7061, 1990). Briefly, ER+/PgR+ indicates the positive staining of 10% to 50% of tumor cell nuclei; 51% to 80% corresponds to ER++/PgR++; and 81% to 100% of stained nuclei indicate a high (ER+++/PgR+++) hormone receptor expression.

Previous or concomitant chemotherapy was not allowed in ABCSG-8. Nodal involvement of a maximum of 10 lymph nodes and an absence of organ metastases had to be determined before trial inclusion. 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 TAM therapy, started within 6 weeks of surgery, or radiotherapy where applicable. Radiotherapy was in general administered according to institutional guidelines; a subprotocol concerning the benefits of radiotherapy in women with node-negative tumors smaller than 3 cm and breast conservation has been previously published (Potter R, Gnant M, Kwasny W, et al: Int J Radiat Oncol Biol Phys 68:334-340, 2007).

Random assignment was performed centrally using a computer-assisted program at the ABCSG-8 randomization center (Vienna, Austria). The following factors were used for stratification: age, grade, tumor size, nodal status, locoregional therapy (modified radical mastectomy $\pm$ radiotherapy, breast-conserving surgery $\pm$ radiotherapy $\pm$ axillary dissection or sentinel lymph node biopsy), hormone receptors, and participating center. Patients were prospectively randomly assigned to receive either 5 years of TAM (20 mg daily) or 2 years TAM (20 mg daily) followed by 3 years of ANA (1 mg daily).

Patient follow-up consisted of physical examination and evaluation of treatment toxicity in 3-month intervals for the first 2 years and 6-month intervals until the fifth year of follow-up. Radiologic assessment routinely consisted of thoracic x-rays and abdominal ultrasound or computed tomography scans in 6-month intervals until year 5. Patients underwent gynecologic examinations every 6 months during their time receiving study medication. Follow-up mammograms were required at yearly intervals. Computed tomography scans, skeletal scintigraphy, and magnetic resonance tomography were additionally ordered whenever clinically indicated. Five years after random assignment, patients underwent full examination and radiologic assessment, as described, in yearly intervals. Differences in adverse event (AE)/serious AE (SAE) rates were tested using χ^2 tests or Fisher's exact tests if appropriate. This was an intention-to-treat (as randomized) safety/toxicity analysis. All SAEs were censored at 60 months.

Section III

SAE groupings:

Uterine disorders. Adenomyosis, adnexa uteri cyst, cervical dysplasia, cervical polyp, cervicitis, cervix carcinoma, cervix disorder, endometrial atrophy, endometrial cancer, endometrial disorder, endometrial dysplasia, endometrial hyperplasia, smear cervix abnormal, uterine cancer, uterine cervix stenosis, uterine disorder, uterine leiomyoma, uterine polyp, uterine prolapse, uterine synechiae, uterovaginal prolapse, vaginal hemorrhage.

Musculoskeletal disorders. Arthralgia, carpal tunnel syndrome, cervicobrachial syndrome, chondromalacia, chondropathy, foot deformity, intervertebral disc protrusion, knee arthroplasty, musculoskeletal pain, osteoarthritis, spinal osteoarthritis, synovitis, tendon rupture, tenosynovitis, tenosynovitis stenosans, trigger finger.

Fracture. Clavicle fracture, facial bone fracture, femoral neck fracture, femur fracture, forearm fracture, fracture delayed union, hip fracture, humerus fracture, lumbar vertebral fracture, osteoporotic fracture, pelvic fracture, pubic rami fracture, radius fracture, rib fracture, skull fractured base, spinal compression fracture, spinal fracture, traumatic fracture, upper limb fracture, wrist fracture.

Cardiovascular and thromboembolic disorders. Acute myocardial infarction, angina pectoris, atrial fibrillation, atrioventricular block complete, cardiac failure, carotid artery stenosis, cerebral hemorrhage, cerebral infarction, cerebrovascular acciden, chest pain, coronary artery disease, deep vein thrombosis, hypertension, hypertensive crisis, myocardial infarction, pelvic venous thrombosis, pulmonary embolism, pulmonary edema, syncope, thrombophlebitis, thrombosis, transient ischemic attack, venous thrombosis, venous thrombosis limb.

Table A1. Predefined AEs

AE	TAM		TAM → ANA		P
	No.	%	No.	%	
Hot flushes	1,259	68.09	1,257	67.40	.65
Vaginal bleeding/discharge	607	32.83	593	31.80	.50
Bone pain	541	29.26	613	32.87	.02
Asthenia, somnolence	314	16.98	340	18.23	.32
Hair loss	247	13.36	274	14.69	.24
Allergy, cutaneous toxicity, skin rash	189	10.22	219	11.74	.14
Nausea	156	8.43	182	9.75	.16
Diarrhea	86	4.65	81	4.34	.65

Abbreviations: AE, adverse event; ANA, anastrozole; TAM, tamoxifen.

Table A2. MedRA-Coded Preferred Terms of SAEs*

SAE	TAM		TAM → ANA		Total		P
	No.	%	No.	%	No.	%	
Carpal tunnel syndrome	4	0.22	23	1.23	27	0.73	< .001†
Cervical polyp	22	1.19	10	0.54	32	0.86	.03
Cervicitis	5	0.27	0	0	5	0.13	.03†
Colonic polyp	13	0.70	3	0.16	16	0.43	.01†
Endometrial atrophy	13	0.70	4	0.21	17	0.46	.03†
Endometrial disorder	89	4.81	54	2.90	143	3.85	< .01
Endometrial hyperplasia	170	9.19	126	6.76	296	7.97	.01
Osteoarthritis	27	1.46	32	1.71	59	1.59	.53
Postmenopausal haemorrhage	24	1.30	25	1.34	49	1.32	.90
Uterine leiomyoma	35	1.89	21	1.13	56	1.51	.06
Uterine polyp	184	9.95	113	6.06	297	7.80	< .001
Vaginal haemorrhage	12	0.65	3	0.16	15	0.40	.02†

Abbreviations: ANA, anastrozole; SAE, serious adverse event; TAM, tamoxifen.
*With > 1% frequency or frequency rate > 0.05 difference or $P < .05$ probability of difference between treatment arms.
†Fisher's exact test.

Table A3. MedRA-Coded Preferred Terms of SAEs Grouped According to Clinical Disease Type

Type of Disorder Leading to SAE	TAM		TAM → ANA		Total	P
	No.	%	No.	%		
Uterine	374	20.23	262	14.05	636	< .001
Musculoskeletal	52	2.81	77	4.13	129	.03
Fracture	28	1.51	43	2.31	71	.08
Cardiovascular/thromboembolic	81	4.38	79	4.24	160	.83

Abbreviations: ANA, anastrozole; SAE, serious adverse event; TAM, tamoxifen.

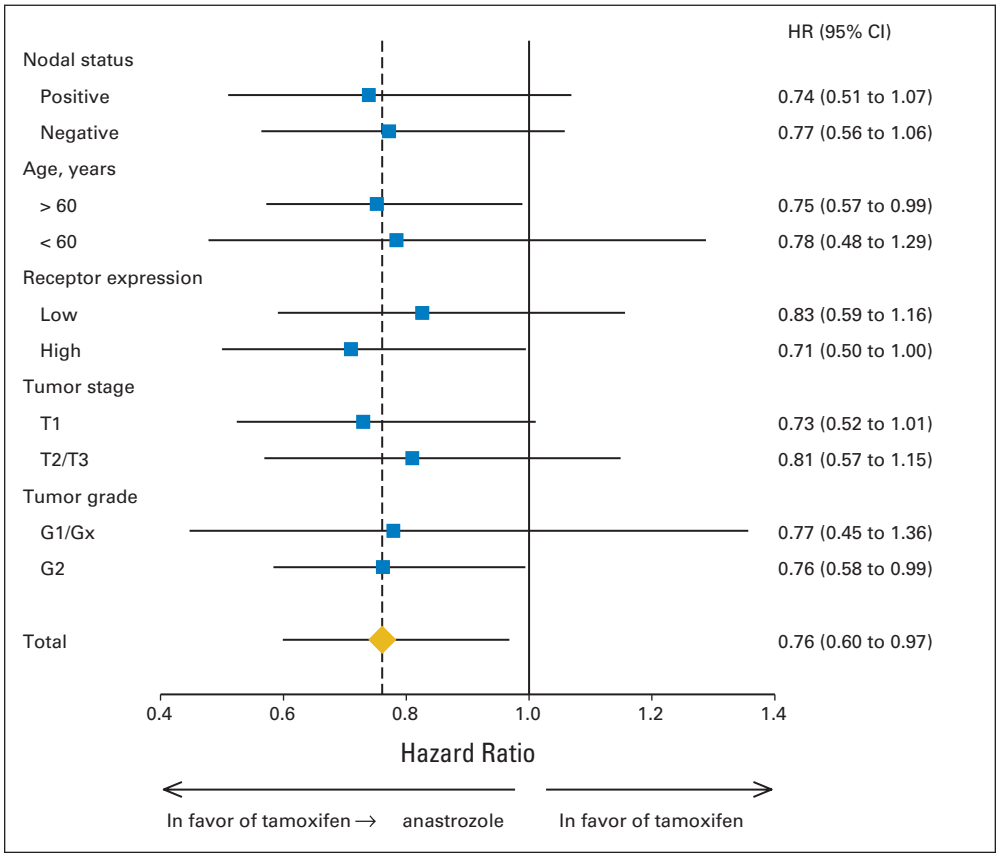

Fig A1. Unadjusted hazard ratios (HRs) in subgroups for recurrence-free survival (censored population).