

Effectiveness of switching from adjuvant tamoxifen to anastrozole in postmenopausal women with hormone-sensitive early-stage breast cancer: a meta-analysis



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Summary

Background For more than 20 years, tamoxifen has been the mainstay of adjuvant endocrine therapy for women with hormone-sensitive early-stage breast cancer. However, not only does tamoxifen have potential side-effects such as an increased risk of endometrial cancer and thromboembolic events, but patients can also develop resistance to the drug. We aimed to investigate whether switching treatment of postmenopausal women with such breast cancer to anastrozole after 2–3 years of tamoxifen would be more effective than continuing on tamoxifen for a total of 5 years.

Methods We did a meta-analysis of three clinical trials—the Austrian Breast and Colorectal Cancer Study Group (ABCSG 8), Arimidex-Nolvadex (ARNO 95), and the Italian Tamoxifen Anastrozole (ITA) studies—in which postmenopausal women with histologically confirmed, hormone-sensitive early-stage breast cancer were randomised to 1 mg/day anastrozole (n=2009) after 2–3 years of tamoxifen treatment or to continued 20 or 30 mg/day tamoxifen (n=1997). We analysed the data with a stratified Cox proportional hazards model with the covariates of age, tumour size, nodal status, grade, surgery, and chemotherapy.

Findings Patients who switched to anastrozole had fewer disease recurrences (92 vs 159) and deaths (66 vs 90) than did those who remained on tamoxifen, resulting in significant improvements in disease-free survival (hazard ratio 0.59 [95% CI 0.48–0.74]; $p < 0.0001$), event-free survival (0.55 [0.42–0.71]; $p < 0.0001$), distant recurrence-free survival (0.61 [0.45–0.83]; $p = 0.002$), and overall survival (0.71 [0.52–0.98]; $p = 0.04$).

Interpretation Our results show that the clinical benefits in terms of event-free survival seen in individual trials for those patients who switched to anastrozole translate into a benefit in overall survival. These findings confirm that clinicians should consider switching postmenopausal women who have taken adjuvant tamoxifen for 2–3 years to anastrozole.

Introduction

Every year, more than 1 million women worldwide are diagnosed with breast cancer, a disease that accounts for almost a quarter of all female cancers.¹ The highest incidence of breast cancer is in developed countries, with more than 360 000 new cases a year in Europe, and more than 200 000 new cases a year in the USA.¹ Although the worldwide incidence of breast cancer continues to rise, perhaps partly as a result of improved screening programmes, mortality rates are beginning to fall because of earlier detection and advances in treatment. At present, 5-year overall survival for women diagnosed with breast cancer is around 75%.¹

For women with early-stage breast cancer, treatment usually begins with surgery (either breast-conserving lumpectomy or mastectomy), with or without radiotherapy or chemotherapy. In women whose tumours are identified as hormone-positive on examination, these initial interventions targeted at removing or destroying the cancerous tissue are often followed by a course of hormone therapy. For more than 20 years, tamoxifen has been the mainstay of adjuvant endocrine therapy for women with hormone-sensitive early-stage breast cancer. Randomised controlled studies show that patients taking tamoxifen for 5 years have better outcomes than those who take tamoxifen for 2 years.^{2,3} However, many of these patients will still develop

and die from metastatic disease within 5 years of their initial diagnosis. But the duration of adjuvant tamoxifen treatment remains in question. Despite its many benefits, it has been associated with various side-effects, including an increased risk of endometrial cancer and thromboembolic events,^{4,6} and resistance to tamoxifen is known to develop in 12–18 months in some patients.⁷

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial,⁸ showed that initial adjuvant treatment of postmenopausal women with early-stage breast cancer with the third-generation aromatase inhibitor anastrozole was more efficacious with a better safety profile than tamoxifen. In addition, several studies^{9–11} have shown the benefits of switching to anastrozole compared with remaining on tamoxifen for 5 years. The results of the combined analysis¹¹ of the Arimidex-Nolvadex (ARNO 95) and Austrian Breast and Colorectal Cancer Study Group (ABCSG 8) trials showed that switching postmenopausal women with hormone-sensitive early-stage breast cancer from tamoxifen to anastrozole after 2 years' adjuvant treatment results in a significant improvement in event-free survival compared with those who continued tamoxifen. Results from the original and updated analyses of the Italian Tamoxifen Arimidex (ITA) trial in node-positive women only^{9,10} also showed significant clinical benefits from switching to anastrozole after 2–3 years of adjuvant tamoxifen.

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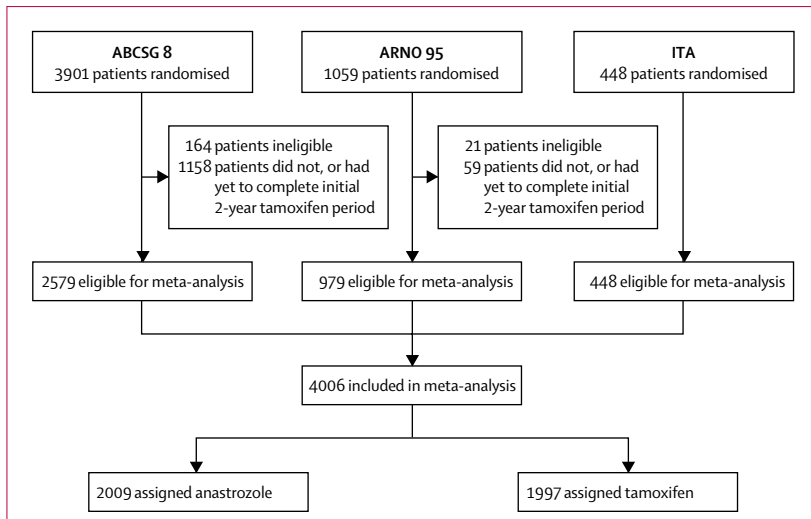


Figure 1: Study profile

Clearly, third-generation aromatase inhibitors have a key role in management of postmenopausal women with early-stage breast cancer, and in 2004, the American Society of Clinical Oncology (ASCO) Technology Assessment recommended that 5 years of tamoxifen alone was no longer the best adjuvant treatment for hormone-sensitive early-stage breast cancer, and that treatment should include use of an aromatase inhibitor to reduce the risk of tumour recurrence.¹² The ASCO assessment favours using the aromatase inhibitor that has been most studied in the setting closest to the individual patient's clinical circumstance.

	Anastrozole 1 mg/day (n=2009)	Tamoxifen 20 mg/day (n=1997)
Age, years	63 (8)*	63 (8)*
Lymph-node status		
Negative	1332 (66%)	1317 (66%)
1-3 nodes positive	532 (27%)	523 (26%)
4-9 nodes positive	123 (6%)	124 (6%)
≥10 nodes positive	21 (1%)	29 (2%)
Not recorded	1 (<1%)	4 (<1%)
Tumour grade		
G1	338 (17%)	339 (17%)
G2	1437 (72%)	1415 (71%)
G3	130 (6%)	137 (7%)
G4	0	1 (1%)
Gx†	101 (5%)	99 (5%)
Unknown	3 (<1%)	12 (<1%)
Previous chemotherapy	148 (7%)	150 (8%)
Surgery		
Breast-conserving‡	1482 (74%)	1478 (74%)
Mastectomy	515 (26%)	502 (25%)
Not recorded or other	12 (1%)	17 (1%)

*Data are mean (SD). †Lobular or unevaluable. ‡Lumpectomy or quadrantectomy.

Table 1: Patient characteristics

	ABCSG 8 (n=2579)	ARNO 95 (n=979)	ITA (n=448)
Node involvement			
Negative	1927 (75%)	720 (74%)	2 (<1%)
Positive	650 (25%)	259 (26%)	443 (99%)
Unknown	2 (<1%)	0	3 (<1%)
Grading	1, 2, or x*	1, 2, 3, or 4	1, 2, 3, or x*
Previous chemotherapy	No	No	Yes†
Surgery			
Breast-conserving	2100 (81%)	673 (69%)	187 (42%)
Mastectomy	478 (19%)	305 (31%)	234 (52%)
Not recorded or other	1 (<1%)	1 (<1%)	27 (6%)

*Lobular or unevaluable. †67% of patients received previous chemotherapy.

Table 2: Differences in patient characteristics between the trials

To increase power and precision, and to help avoid bias or random error, we aimed to do a meta-analysis to compare the effect of switching postmenopausal women with hormone-sensitive early-stage breast cancer to anastrozole after 2–3 years of tamoxifen with being treated with tamoxifen for 5 years.

Methods

Search strategy and selection criteria

Trials were identified from the PubMed and ClinicalTrials.gov databases using the keywords aromatase inhibitor, anastrozole, letrozole, and exemestane from Jan 1, 2004, to March 31, 2005. Studies were eligible if they were phase III trials in which postmenopausal women with histologically confirmed, hormone-positive early-stage breast cancer were randomised to a third-generation aromatase inhibitor or to continued tamoxifen after 2–3 years of adjuvant tamoxifen.^{9,11} Trials were excluded if they assessed a steroidal aromatase inhibitor, or if they did not use tamoxifen as the comparator group.

Endpoints

The endpoints for the meta-analysis were disease-free survival (defined as time to relapse at any site, incidence of contralateral breast cancer, or death from any cause), event-free survival (defined as time to relapse at any site or incidence of contralateral breast cancer), distant-recurrence-free survival (defined as time to the earliest occurrence of distant recurrence), and overall survival (including deaths with or without recurrence).

Statistical analysis

Individual patient data were analysed with a stratified Cox-proportional hazards model (in which each trial was a stratum) with the covariates of age, tumour size, nodal status, grade, surgery, and chemotherapy. Data were analysed independently by IZ and MG; no discrepancies arose. Analyses were undertaken with Statistical Analysis System (SAS) software version 8.01, and allowed for a specific hazard ratio (ie, risk of recurrence or death) for differing

levels of each covariate (eg, node-positive or node-negative), and, as each individual trial was a stratum, for each of the three trials. Stratifying by trial ensured that patients were compared with others in the same trial, and then combined to produce the required summary comparison between anastrozole and tamoxifen across the three trials.

Thus, hazard ratios were calculated for disease-free, event-free, distant recurrence-free, and overall survival. In addition, forest plots were generated to summarise individual and overall trial data, and Kaplan-Meier curves were generated for each endpoint. A basic test for heterogeneity using summary statistics from the individual trials was done, and showed no heterogeneity ($p>0.1$). Given this result and the limited number of trials, no further tests for heterogeneity were done.

Since the purpose of a meta-analysis is to summarise all the trials of one treatment compared with another in a single comparison, no correction for multiple comparisons was necessary. The trials are registered with Clinical Trials.gov: ABCSG 8, NCT00291759; ARNO 95, NCT00287534; and ITA, NCT00286117.

Role of the funding source

Statisticians from AstraZeneca and SKM analysed all data. AstraZeneca funded a medical writer to prepare references, figures, tables, technical editing for English language, formatting, and administrative support. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the report for publication.

Results

Five trials were identified in which patients were randomly allocated to tamoxifen or an aromatase inhibitor after initial treatment with tamoxifen. One trial was excluded because it investigated a steroidal aromatase inhibitor, and one other trial was excluded because the aromatase inhibitor (letrozole) was compared with placebo rather than tamoxifen. Three trials—the ABCSG 8, ARNO 95, and ITA—therefore met the eligibility criteria, all of which are included in this meta-analysis. The ARNO 95 and ITA trials were randomised after patients had completed the initial tamoxifen period. Patients in the ABCSG 8 trial were randomised at diagnosis, before the initial tamoxifen period but data were analysed only from the point of switch—ie, from patients receiving randomised treatment after the initial tamoxifen period. At the cut-off of March 31, 2005, all trials that met these criteria had investigated the aromatase inhibitor anastrozole.

4006 eligible patients were included in the meta-analysis: 2579 patients from ABCSG 8, 979 patients from ARNO 95, and 448 patients from ITA (figure 1). The treatment groups were broadly similar across the three studies for all demographic and baseline breast cancer characteristics assessed (table 1). Key differences between the trial populations are detailed in table 2.

Patients who completed 2–3 years of adjuvant tamoxifen therapy and were relapse-free were randomised to either continue tamoxifen (20 or 30 mg/day) or switch to anastrozole (1 mg/day) for the remainder of their treatment (5 years in total). In the first year after the switch point,

	Anastrozole 1 mg/day (n=2009)	Tamoxifen 20 mg/day (n=1997)
Local recurrence, n (%)	19 (1%)	35 (2%)
Distant recurrence, n (%)	59 (3%)	102 (5%)
Contralateral breast cancer, n (%)	14 (1%)	22 (1%)
Total recurrence events, n (%)	92 (5%)	159 (8%)
Disease-free survival events	125	199
Deaths		
After recurrence	33	50
Without recurrence	33	40
All	66	90
Deaths in individual studies (after recurrence/without recurrence)		
ABCSG 8	14/28	17/27
ARNO 95	13/2	19/9
ITA	6/3	14/4

Table 3: First recorded event (local or distant recurrence or incidence of new contralateral breast cancer) and all observed deaths

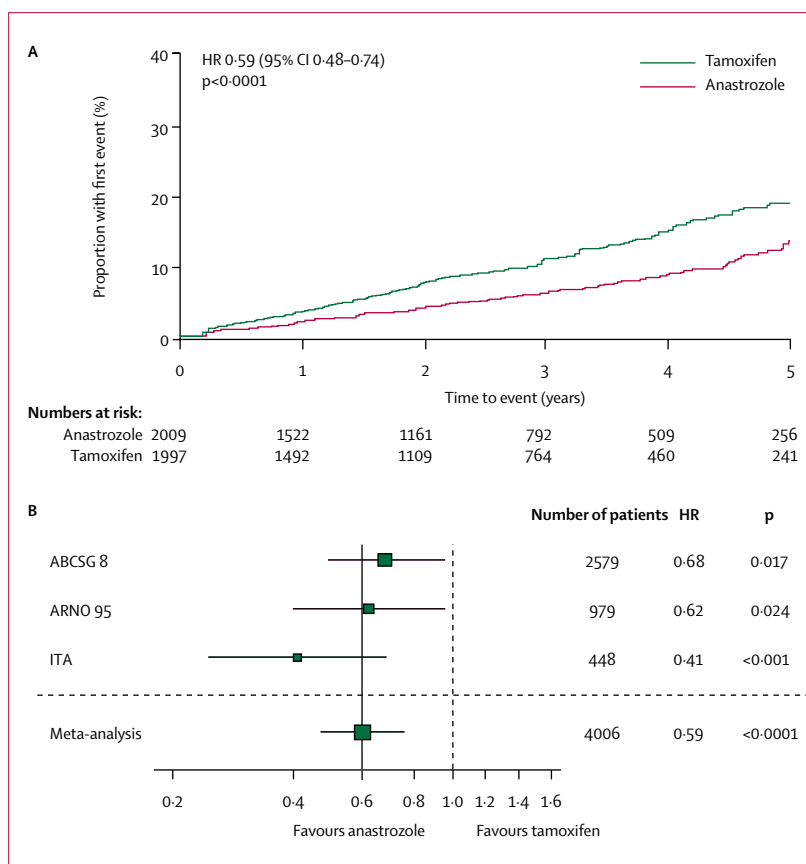


Figure 2: Kaplan-Meier curve (A) and forest plot (B) of disease-free survival in anastrozole or tamoxifen-only groups

HR=hazard ratio.

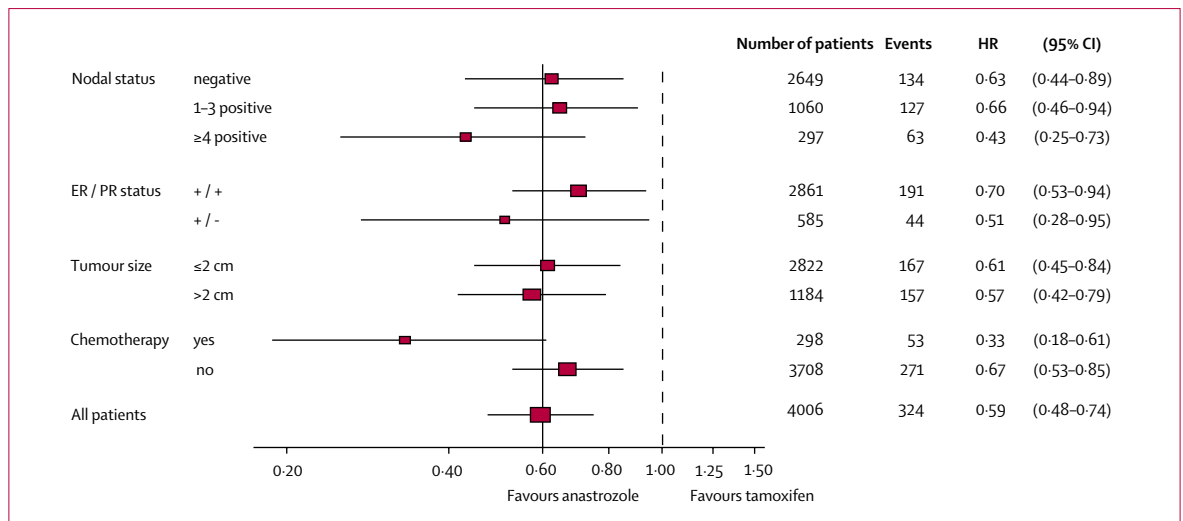


Figure 3: Forest plot of disease-free survival in subgroups of anastrozole or tamoxifen-only groups
ER=oestrogen receptor. PR=progesterone receptor. HR=hazard ratio.

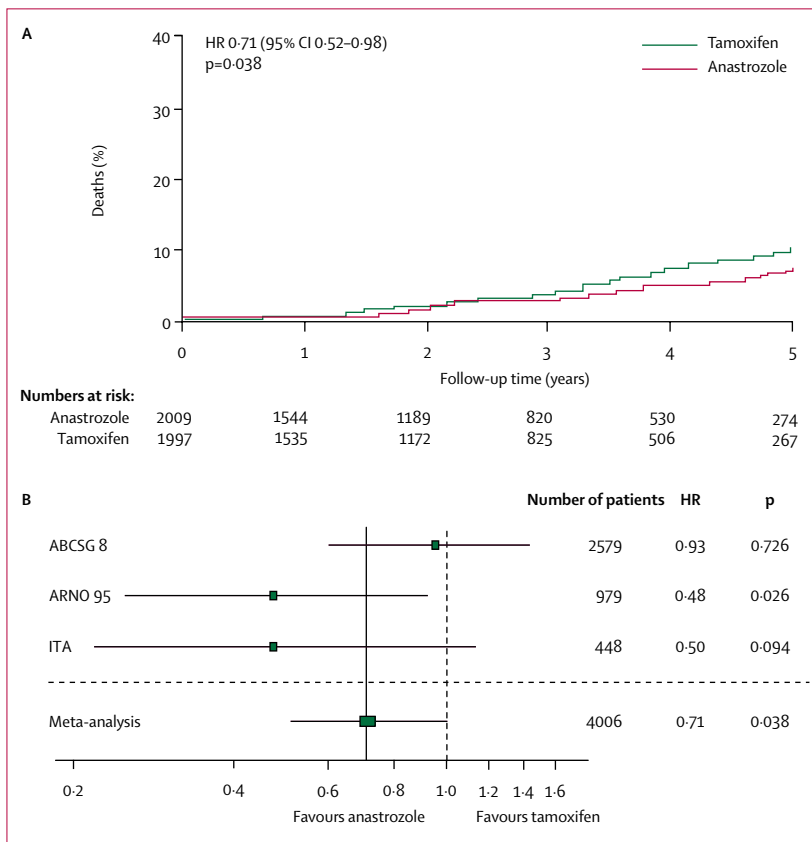


Figure 4: Kaplan-Meier curve (A) and forest plot (B) of overall survival in anastrozole or tamoxifen-only groups
HR=hazard ratio.

patients underwent clinical examination every 3 months in the ABCSG 8 and ITA trials; subsequent examinations were done every 6 months in the ITA trial and at 6-monthly

intervals in the second and third year of the ABCSG 8 trial, and yearly thereafter. In the ARNO 95 trial, patients were assessed at 6-monthly intervals. All three studies assessed local and distant recurrence, contralateral breast cancers, and all deaths (deaths following recurrence and deaths without recurrence). Median follow-up for each individual study was: ABCSG 8, 24.4 months (range 0.0-84.4); ARNO 95, 32.7 months (0.0-89.5); and ITA, 50.4 months (0.0-79.8). Median follow-up for the meta-analysis was 30 months (0-89.5), with a total duration of follow-up of 5389 person-years for the anastrozole group and 5339 person-years for the tamoxifen group.

Patients who were switched to anastrozole had fewer recurrences (92 [5%] vs 159 [8%]) and deaths (66 [3%] vs 90 [5%]) than did those who remained on tamoxifen (table 3). Switching to anastrozole resulted in a significant improvement in disease-free survival, with hazard ratio for recurrence or death of 0.59 (95% CI 0.48-0.74; $p < 0.0001$) for switching to anastrozole compared with continuing on tamoxifen (figure 2). The benefit of anastrozole over tamoxifen was evident irrespective of nodal or receptor status, previous chemotherapy, or tumour size (figure 3). Patients who switched to anastrozole also had significant improvements in event-free survival (0.55 [0.42-0.71]; $p < 0.0001$), distant recurrence-free survival (0.61 [0.45-0.83]; $p = 0.0015$) and overall survival (0.71 [0.52-0.98]; $p = 0.0377$) compared with those continuing on tamoxifen (figure 4).

Discussion

Our results show that patients who switched to anastrozole after 2-3 years of tamoxifen have significantly fewer disease recurrences than do those who remain on tamoxifen. Disease-free and event-free survival, including the occurrence of contralateral breast cancer and distant metastases, were significantly improved in those who switched

to anastrozole. Additionally, switching therapy resulted in a significant advantage in overall survival compared with continued tamoxifen.

The ITA patient population had different characteristics to the ABCSG 8 and ARNO 95 populations. Most patients were node-positive in the ITA trial compared with a node-negative majority in the ABCSG 8 and ARNO 95 trials. In addition, more patients in the ITA trial had undergone a mastectomy and had received chemotherapy than had those in ABCSG 8 and ARNO 95. However, these differences should not affect our outcome, since this meta-analysis used individual patient data, which increases the power of the individual studies and strengthens the biometric power of the dataset. Indeed, the benefit of anastrozole over tamoxifen was evident irrespective of nodal status, tumour size, or whether the patient had received chemotherapy. Although all three studies showed a benefit for anastrozole, a difference in prognosis in the ABCSG 8 trial led to more deaths without recurrence, and thus a hazard ratio closer to 1.00. Importantly, fewer women died in the anastrozole group than in the tamoxifen group both from breast cancer and non-breast cancer causes.

The results of one further randomised controlled trial (Intergroup Exemestane Study [IES])^{13,14} investigating the benefit of switching from tamoxifen to an aromatase inhibitor after 2–3 years of adjuvant therapy in postmenopausal women with early-stage, hormone-sensitive breast cancer, has been reported. This study was excluded from the meta-analysis because the aromatase inhibitor involved was steroidal and therefore did not meet our inclusion criteria. We did not include steroidal aromatase inhibitors because differences in the pharmacological and pharmacokinetic profiles between the two types of these drugs could translate into clinical differences.^{15–18} However, the results are mostly consistent with those presented here. At 58 months' median follow-up, disease-free survival, time to contralateral breast cancer, and time to distant recurrence were significantly better in women who switched to exemestane compared with those who remained on tamoxifen, although the hazard ratio for overall survival was 0.85 (95% CI 0.71–1.02; $p=0.08$) in the intent-to-treat population.¹⁴ On excluding 122 oestrogen receptor-negative patients, the hazard ratio for overall survival in women with oestrogen receptor-positive or receptor-status-unknown disease was 0.83 (0.69–1.00; $p=0.05$).¹⁴

Whether aromatase inhibitors should be offered as initial adjuvant treatment, or after 2 or more years of tamoxifen, remains uncertain. A modelling study¹⁹ by Punglia and colleagues concluded that a switching strategy would be best. However, since this model did not account for the different endpoints in the individual trials, the benefits of a switching strategy will have been exaggerated. For instance, use of disease-free survival as an endpoint can dilute the results. By contrast, another modelling study²⁰ by Cuzick and co-workers, which used the more sensitive efficacy endpoint of recurrence, and allowed for the timing of

events, has suggested that use of an aromatase inhibitor as initial adjuvant treatment is a better option than switching patients to an aromatase inhibitor after 2 or more years of tamoxifen.

Clearly, real data from well-designed clinical trials are needed to inform treatment strategies. The data included in this meta-analysis are only for the time of switched treatment, and are thus not directly relevant to a prospective treatment strategy of commencing with tamoxifen with the intention of changing to an aromatase inhibitor after 2 or more years. However, the survival benefit that emerged from our analysis—and so far not present in any trial that assessed aromatase inhibitors as initial adjuvant treatment—suggests that a tamoxifen induction period could be beneficial, despite the fact that relapse rates might be highest in the first 2 years. This issue will be resolved only by prospective evaluation of treatment strategies, as is being done in trials such as the Breast International Group (BIG) 1-98 trial investigating the aromatase inhibitor letrozole.

Efficacy in trials of aromatase inhibitors is generally defined in terms of disease-free survival, and no significant overall survival benefit has yet been established in trials investigating aromatase inhibitors in the adjuvant treatment of early-stage breast cancer, except in a subset of patients with node-positive disease in the National Cancer Institute of Canada MA 17 trial²¹ in the extended adjuvant treatment setting, comparing letrozole with placebo, rather than with tamoxifen. Although disease-free survival has been accepted as a good surrogate for overall survival in chemotherapy trials, that assumption might not be accurate in trials of aromatase inhibitors, mainly because of the many non-breast-cancer deaths. The low and constant rate of disease-free survival events in study populations, coupled with the relatively small differences (in absolute terms) compared with tamoxifen, and the relatively good prognosis of patients, might ultimately restrict the ability to detect a benefit in overall survival, even assuming that aromatase inhibitors are more active than tamoxifen. In a study comparing tamoxifen with placebo in patients with lymph-node-negative early-stage breast cancer, overall survival benefits were not seen in individuals for at least 7 years, and a significant difference in overall survival was not seen for 10 years.^{22,23} Thus, a meta-analysis might be the only way to detect an overall survival benefit in adjuvant aromatase inhibitor trials that compare active treatments.

Safety and tolerability are key considerations for any adjuvant drug used in long-term treatment. In a previous study⁸ of initial adjuvant treatment, patients treated with anastrozole for the full 5-year treatment period had significantly fewer thromboembolic and cerebrovascular events and uterine carcinoma than did those treated with tamoxifen, although they had significantly more fractures and joint symptoms. Overall, there were significantly fewer serious adverse events, drug-related adverse events, and withdrawals due to adverse events in patients treated with

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anastrozole compared with those treated with tamoxifen. Although a detailed analysis of the safety profiles of anastrozole and tamoxifen was beyond the scope of the present meta-analysis, the safety profiles for anastrozole and tamoxifen in the individual studies were consistent with those previously reported in postmenopausal women with hormone receptor-positive early-stage breast cancer,⁹⁻¹¹ and no new safety issues were identified within the context of switching therapy after 2–3 years.²⁴

For the past few decades, 5 years' adjuvant tamoxifen therapy after primary treatment has been the gold standard for treating postmenopausal women with hormone-sensitive early-stage breast cancer. However, guidelines such as those produced by ASCO¹² now recommend that ideally, adjuvant hormonal treatment in such women should include an aromatase inhibitor as initial treatment or after tamoxifen. The National Comprehensive Cancer Network (NCCN) guidelines²⁵ recommend switching to anastrozole after initial 2–3 years' tamoxifen (for a complete course of 5 years' hormonal therapy) in postmenopausal women, and the St Gallen Expert consensus²⁶ also supports the use of adjuvant AIs. Our findings further challenge the existing standard clinical approach of 5 years' adjuvant tamoxifen therapy.

Contributors

W Jonat contributed to data collection, development of the analysis plan, and writing of the report. M Gnant contributed to the collection of data, development of analysis plan, and writing of the report. F Boccardo participated in study planning, presentation and interpretation of results, and writing of the report. M Kaufmann is chairman of the ARNO 95 trial and participated in the discussion of the report. A Rubagotti contributed to study planning, reviewing results, and writing of the report. I Zuna and M Greenwood analysed the data. R Jakesz was principal investigator of the Austrian trial and contributed to the design and presentation of this study.

Conflicts of interest

W Jonat, R Jakesz, and M Kaufmann have done research sponsored by AstraZeneca. M Kaufmann has received honoraria from AstraZeneca, Pfizer, and Novartis. F Boccardo has received travel grants and honoraria from AstraZeneca. M Gnant has received research support, travel grants, and honoraria from Novartis, AstraZeneca, Pfizer, Roche, and Sanofi-Aventis. M Greenwood is an employee of AstraZeneca. A Rubagotti and I Zuna declare no conflicts of interest.

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References

- Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005; **55**: 74–108.
- Current Trials Working Party of the Cancer Research Campaign in Breast Cancer Trials Group. Preliminary results from the cancer research campaign trial evaluating tamoxifen duration in women aged fifty years or older with breast cancer. *J Natl Cancer Inst* 1996; **88**: 1834–39.
- Swedish Breast Cancer Cooperative Group. Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. *J Natl Cancer Inst* 1996; **88**: 1543–49.
- 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.
- Fisher B, Costantino JP, Redmond CK, et al. 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.
- Gradishar W. Safety considerations of adjuvant therapy in early breast cancer in postmenopausal women. *Oncology* 2005; **69**: 1–9.
- Dorssers LC, Van der Flier S, Brinkman A, et al. Tamoxifen resistance in breast cancer: elucidating mechanisms. *Drugs* 2001; **61**: 1721–33.
- 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.
- 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 trial. *J Clin Oncol* 2005; **23**: 5138–47.
- Boccardo F, Rubagotti A, Puntoni M, and other ITA trialists. Switching to anastrozole (ANA) vs continued tamoxifen (TAM) treatment of early breast cancer (EBC). Updated results of the Italian tamoxifen anastrozole (ITA) trial. *Proc Am Soc Clin Oncol* 2005; **23**: 10s (abstr).
- Jakesz R, Jonat W, Gnant M, for the ABCSG and the GABG. 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. *Lancet* 2005; **366**: 455–62.
- 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.
- 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.
- Coombes RC, Paridaens R, Jassem J, et al for the Intergroup Exemestane Study (IES). First mature analysis of the Intergroup Exemestane Study. *Proc Am Soc Clin Oncol* 2006; **24** (abstr).
- Buzdar A, Robertson JFR, Eiermann W, Nabholz JM. An overview of the pharmacology and pharmacokinetics of the newer generation aromatase inhibitors anastrozole, letrozole and exemestane. *Cancer* 2002; **95**: 2006–16.
- McCloskey E, Eastell R, Lakner G, et al. Initial results from the LEAP study: the first direct comparison of safety parameters between aromatase inhibitors in healthy postmenopausal women. *Breast Cancer Res Treat* 2005; **94**: S101 (abstr).
- McCloskey E. Effects of third-generation aromatase inhibitors on bone. *Eur J Cancer* 2006; **42**: 1044–51.
- Nabholtz JM, Gligorov J. Cardiovascular safety profiles of aromatase inhibitors: a comparative review. *Drug Safety* 2006; **29**: 785–801.
- Punglia RS, Kuntz KM, Winer EP, et al. Optimizing adjuvant endocrine therapy in postmenopausal women with early-stage breast cancer: a decision analysis. *J Clin Oncol* 2005; **23**: 5178–87.
- Cuzick J, Sasieni P, Howell A. Should aromatase inhibitors be used as initial adjuvant treatment or sequenced after tamoxifen? *Br J Cancer* 2006; **94**: 460–64.
- Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005; **97**: 1262–71.
- 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.
- Fisher B, Jeong JH, Dignam J, et al. Findings from recent National Surgical Adjuvant Breast and Bowel Project adjuvant studies in stage I breast cancer. *J Natl Cancer Inst Monogr* 2001: 62–66.
- Buzdar AU. Role of anastrozole in adjuvant therapy for postmenopausal patients. *Semin Oncol* 2003; **30** (suppl 16): 21–29.
- National Comprehensive Cancer Network. NCCN practice guidelines in oncology v.2.2006: breast cancer. <http://www.nccn.org> (accessed July 24, 2006).
- Goldhirsch A, Glick JH, Gelber RD, et al. Meeting highlights: international expert consensus on the primary therapy of early breast cancer 2005. *Ann Oncol* 2005; **16**: 1569–83.