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The use of aromatase inhibitors in adjuvant therapy for early breast cancer

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Abstract Clinical evidence supporting the use of aromatase inhibitors (AIs) in adjuvant therapy for hormone-sensitive early breast cancer (EBC) has grown rapidly over the past few years and is reviewed in this article. The results of two studies—the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial and the Breast International Group (BIG) 1-98 trial—support the use of AIs as primary adjuvant therapy for EBC, with significantly prolonged disease-free survival, time to recurrence, and time to distant recurrence for both anastrozole and letrozole over tamoxifen. Furthermore, anastrozole has an established beneficial risk:benefit ratio compared with tamoxifen with mature data over the full 5-year recommended treatment period. For women who have already received 2–3 years of tamoxifen, switching studies with anastrozole [the Italian Tamoxifen Anastrozole (ITA) trial and the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8/Arimidex-Nolvadex (ARNO 95) trial] and exemestane [the Intergroup Exemestane Study (IES)] have also shown that 5 years of primary adjuvant tamoxifen therapy is not optimal and that switching to an AI should be considered. Finally, for those women who have completed 5 years of tamoxifen, based on the results of the MA 17 trial, extended adjuvant treatment with letrozole should be considered. Although no sequencing data are available yet, current evidence suggests that an AI should be the adjuvant treatment of choice over tamoxifen, and anastrozole is the only AI with mature adjuvant data to date.

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Introduction

Five years of tamoxifen has been the standard adjuvant endocrine treatment for hormone-sensitive early breast cancer (EBC) for almost 30 years, but better-tolerated alternatives with improved efficacy have been sought to improve prognosis for postmenopausal women diagnosed with EBC. Although adjuvant tamoxifen decreases the risk of recurrence for postmenopausal women by around 50% [8], long-term tamoxifen use also increases the risk of endometrial cancer by up to four-fold over this time [8], with no additional benefit gained from extending treatment beyond 5 years [9].

Clinical evidence supporting the use of aromatase inhibitors (AIs) in adjuvant therapy for hormone-sensitive EBC has grown rapidly over the past few years. Unlike tamoxifen, which inhibits the oestrogen receptor pathway and transcription of oestrogen-regulated genes, AIs prevent synthesis of oestrogen by inhibiting the aromatase enzyme that catalyses the conversion of androgens to oestrogens. Clinical development has led to the availability of three third-generation AIs: anastrozole and letrozole (both non-steroidal AIs) and exemestane (a steroidal AI). Initially tested and used in the treatment of postmenopausal women as first- or second-line treatment for advanced breast cancer, the most recent advances have been made in the use of third-generation AIs as adjuvant therapy for EBC. Clinical trials have assessed the efficacy and safety of AIs compared with tamoxifen as: primary adjuvant therapy for newly diagnosed women with EBC; an alternative for women who have already received 2–3 years of prior adjuvant tamoxifen; and extended adjuvant therapy for women who have completed 5 years of adjuvant tamoxifen. In this article, these recent clinical trial results and their implications for clinical practice are discussed.

Primary aromatase inhibitor adjuvant therapy for newly diagnosed women

Results are available from two studies that have investigated the use of AIs as primary adjuvant therapy for postmenopausal women with newly diagnosed EBC. For the first of these studies, the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which compared anastrozole versus tamoxifen, mature results have been published at a median follow-up of 68 months [3]. For the second study, the Breast International Group (BIG) 1-98 trial, which compared letrozole versus tamoxifen, initial results at a median follow-up of 26 months were presented at the ninth International Conference on the Primary Therapy of Early Breast Cancer in St Gallen, Switzerland, in January 2005 [4].

The ATAC trial

The ATAC trial compared anastrozole with tamoxifen as initial adjuvant treatment in 9,366 postmenopausal women with EBC, of whom 84% were hormone receptor-positive [1–3]. Primary endpoints were disease-free survival (defined as the time to earliest occurrence of local or distant recurrence, new primary breast cancer, or death from any cause) and tolerability.

Data covering the entire 5-year adjuvant period (median follow-up 68 months) confirmed improved efficacy and superior tolerability of anastrozole compared with tamoxifen. Patients receiving anastrozole had significantly prolonged disease-free survival [575 vs. 651 events; hazard ratio (HR) 0.87; 95% confidence intervals (CI) 0.78, 0.97; $P = 0.01$], time to recurrence (402 vs. 498 events; HR 0.79; 95% CI 0.70, 0.90; $P = 0.0005$), and time to distant recurrence (324 vs. 375 events; HR 0.86; 95% CI 0.74, 0.99; $P = 0.04$), with greater advantages seen in patients with hormone receptor-positive disease (Figs. 1, 2). Patients receiving anastrozole also had significantly reduced incidence of contralateral breast cancers (35 vs. 49; 42% reduction; 95% CI 12–62%; $P = 0.01$). Overall survival was similar between the treatment groups. However, since the trial population had a relatively good prognosis (61% lymph node-negative, 64% tumours ≤ 2 cm in diameter), it is too early to expect a difference in survival. For example, the National Surgical Adjuvant Breast Project (NSABP) B-14 trial that compared tamoxifen versus placebo took >7 years to show a statistically significant survival advantage for tamoxifen over placebo [10, 11].

Since almost all of the patients in the ATAC trial completed their scheduled 5 years of therapy (only 8% of patients remained on trial treatment at this follow-up), the safety and tolerability data can be considered final. Treatment with anastrozole was associated with significant reductions of incidence of endometrial cancer, thromboembolic events, ischemic cerebrovascular events, hot flushes, vaginal bleeding and vaginal discharge compared with tamoxifen (Table 1). Treatment with tamoxifen was associated with less arthralgia and fewer fractures than treatment with anastrozole; however, the incidence of hip fractures, a fracture type with a high morbidity, was similar between the two treatment groups.

Table 1 Pre-specified adverse events in the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial at a median follow-up of 68 months. Reprinted with permission of Elsevier from ATAC Trialists' Group [3]

Adverse event	Patients, %		OR[a] (95% CI)	*P* value
	Anastrozole ($n = 3,092$)	Tamoxifen ($n = 3,094$)		
Hot flushes	35.7	40.9	0.80 (0.73, 0.89)	<0.0001
Arthralgia	35.6	29.4	1.32 (1.19, 1.47)	<0.0001[b]
Vaginal bleeding	5.4	10.2	0.50 (0.41, 0.61)	<0.0001
Vaginal discharge	3.5	13.2	0.24 (0.19, 0.30)	<0.0001
Endometrial cancer[c]	0.2	0.8	0.29 (0.11, 0.80)	0.02
Fractures[d]	11.0	7.7	1.49 (1.25, 1.77)	<0.0001[b]
Hip	1.2	1.0	1.20 (0.74, 1.93)	0.5
Spine	1.5	0.9	1.68 (1.04, 2.71)	0.03[b]
Wrist/colles	2.3	2.0	1.15 (0.81, 1.64)	0.4
All other sites[e]	7.1	4.6	1.59 (1.28, 1.98)	<0.0001[b]
Ischemic cardiovascular disease	4.1	3.4	1.23 (0.95, 1.60)	0.1
Ischemic cerebrovascular events	2.0	2.8	0.70 (0.50, 0.97)	0.03
Venous thromboembolic events	2.8	4.5	0.61 (0.47, 0.80)	0.0004
Deep venous thromboembolic events	1.6	2.4	0.64 (0.45, 0.93)	0.02

Nausea and vomiting, fatigue/tiredness, mood disturbances, and cataracts were also pre-specified adverse events but there were no significant differences between the treatment groups in these adverse events

CI Confidence intervals

[a]Odds ratio (anastrozole vs. tamoxifen)

[b]In favour of tamoxifen

[c] $n = 2,229$ for anastrozole and $n = 2,236$ for tamoxifen (excluding patients with hysterectomy at baseline), recorded at any time

[d]Patients with ≥1 fracture occurring at any time before recurrence (includes patients no longer receiving treatment)

[e]Patients may have had ≥1 fracture at different sites

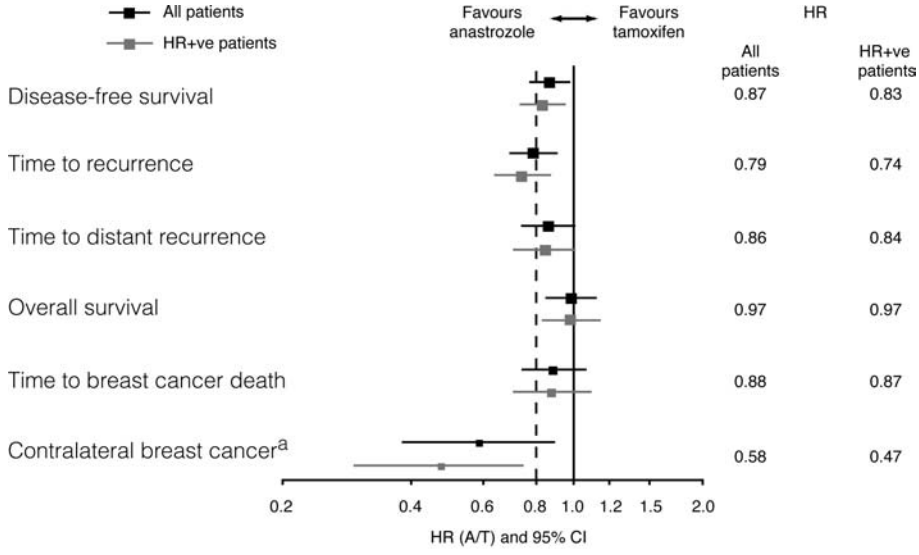


Fig. 1 Efficacy results of the Armidex, Tamoxifen, Alone or in Combination (ATAC) trial at a median follow-up of 68 months. Reprinted with permission of Elsevier from ATAC Trialists' Group [3]

[a]Odds ratio calculated rather than HR
A, anastrozole; CI, confidence intervals; HR, hazard ratio; HR+ve, hormone receptor-positive; T, tamoxifen

The results of the ATAC trial provide the largest safety database for any of the third-generation AIs and highlight that anastrozole has a consistent beneficial risk:benefit ratio compared with tamoxifen as initial adjuvant treatment.

The Breast International Group (BIG) 1-98 Trial

Early efficacy data from the BIG 1-98 Trial, which compared letrozole with tamoxifen as adjuvant therapy, has further strengthened the clinical evidence supporting the initial use of AIs in this setting. In this trial, patients were randomised to 5 years of tamoxifen or 5 years of letrozole (two-arm option) and to 2 years of tamoxifen followed by 3 years of letrozole or 2 years of letrozole followed by 3 years of tamoxifen (four-arm option). The primary endpoint was disease-free survival (defined as for the ATAC trial with the addition of non-breast second primaries).

A total of 8,028 postmenopausal women were randomised: 1,835 to the two-arm option and 6,193 to the four-arm option [4]. All patients were hormone receptor-positive; 59% were node-negative and 63% had a tumour ≤ 2 cm in diameter. The primary core analysis, comparing letrozole versus tamoxifen as primary adjuvant therapy, included events in the two-arm option as well as in the switching arms up to treatment switch plus 30 days. Sequencing data from the BIG 1-98 trial are yet to be reported.

At a median follow-up of 26 months, letrozole significantly prolonged disease-free survival, time to recurrence and time to distant recurrence, compared with tamoxifen (Table 2). There was no significant difference in overall survival. There was a significant reduction of incidence of grade 3–5 thromboembolic events in the letrozole group (odds ratio 0.38; $P < 0.0001$) compared with the tamoxifen group. However, significantly, more patients treated with letrozole had bone fractures compared with tamoxifen (odds ratio 1.44; $P = 0.0006$) and more patients died

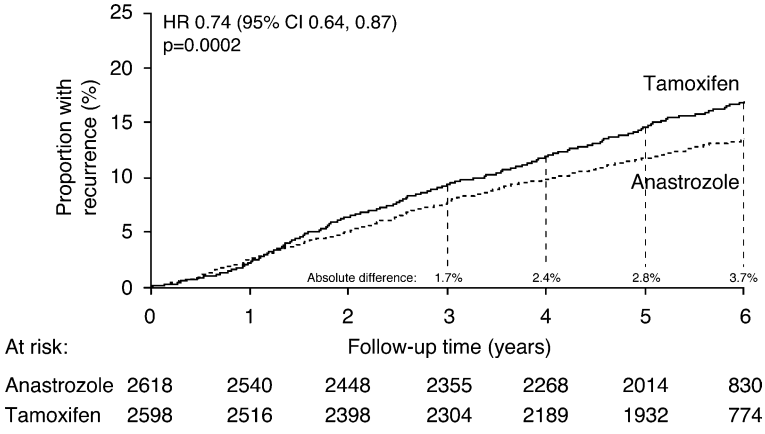


Fig. 2 Kaplan–Meier probability of time to recurrence in hormone receptor-positive patients in the Armidex, Tamoxifen, Alone or in Combination (ATAC) trial at a median follow-up of 68 months. Reprinted with permission of Elsevier from ATAC Trialists' Group [3]

CI, confidence intervals; HR, hazard ratio

Table 2 Summary of efficacy results of the Breast International Group (BIG) 1-98 trial at median follow-up of 26 months [4]

	Letrozole vs. tamoxifen (No. of events)	HR (95% CI)	*P* value
Disease-free survival	351 vs. 428	0.81 (0.70, 0.93)	0.003
Disease-free survival excluding non-breast second primaries[a]	296 vs. 369	0.79 (0.68, 0.92)	0.002
Time to recurrence	228 vs. 310	0.72 (0.61, 0.86)	0.0002
Time to distant recurrence	184 vs. 249	0.73 (0.60, 0.88)	0.0012
Overall survival	166 vs. 192	0.86 (0.70, 1.06)	0.16

[a]ATAC definition of disease-free survival

without recurrence in the letrozole group (55 vs. 38 patients; $P = 0.08$), the difference being due to cerebrovascular (7 vs. 1) and cardiac (26 vs. 13) deaths.

These results further support the use of AIs as primary adjuvant therapy for EBC over tamoxifen. However, the data for letrozole are not mature and the long-term risk:benefit profile has not yet been established. The American Society of Clinical Oncology (ASCO) technology assessment "favours using the aromatase inhibitor that has been studied in the setting most closely approximating any individual patient's clinical circumstance" [16]. Since anastrozole is the only AI that has been studied over the full 5-year recommended adjuvant-treatment period, it should be the preferred initial treatment for postmenopausal women with hormone receptor-positive EBC.

Switching to aromatase inhibitor in women already receiving adjuvant tamoxifen

Further studies have investigated the option of switching therapy to an AI as a strategy to improve outcomes for women already receiving adjuvant tamoxifen. Both the Italian Tamoxifen Anastrozole (ITA) trial [5] and Austrian Breast and Colorectal Cancer Study Group (ABCSG) 8/Arimidex-Nolvadex (ARNO) 95 combined analysis [14] investigated switching postmenopausal women with hormone-sensitive EBC to anastrozole after 2–3 years of adjuvant tamoxifen compared with continuing tamoxifen treatment. The switching approach has also been investigated with the steroidal AI exemestane in the International Exemestane Study (IES) [6].

The Italian Tamoxifen Anastrozole (ITA) trial

The ITA trial enrolled 448 postmenopausal women with node-positive, oestrogen receptor-positive tumours who had already received 2–3 years of adjuvant tamoxifen [5]. At a median follow-up of 36 months, 45 events had been reported in the tamoxifen group compared with 17 in the anastrozole group. There were significant increases of recurrence-free and local recurrence-free survival in the anastrozole group (HR 0.35; 95% CI 0.18, 0.68; $P = 0.001$ and HR 0.15; 95% CI 0.03, 0.65; $P = 0.003$, respectively), and the difference in distant metastases-free survival approached statistical significance (HR 0.49; 95% CI 0.22, 1.05; $P = 0.06$) [5].

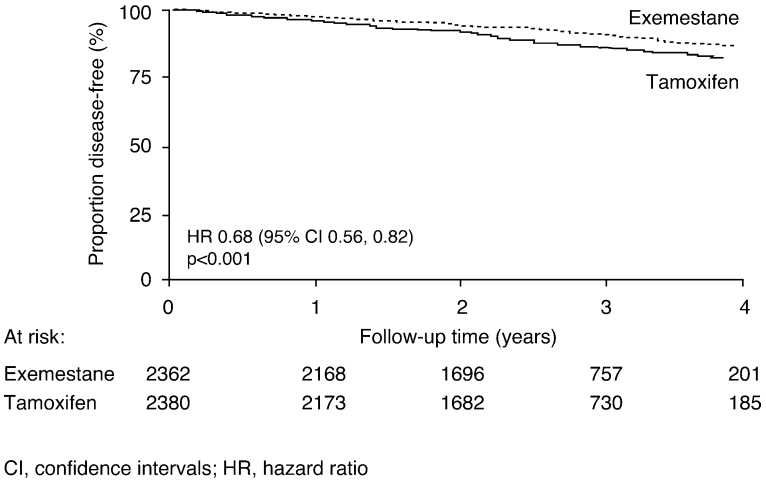
The ABCSG 8/ARNO 95 trials

The ABCSG 8/ARNO 95 trials were prospectively designed for combined analysis. The combined analysis included 3,123 randomised patients, of whom 100% had hormone receptor-positive disease and 27% were node-positive. In this trial, patients were randomised to anastrozole or continued tamoxifen after 2 years of tamoxifen therapy. At a median follow-up of 26 months, after 143 events had been reported, there was a significant increase of recurrence-free survival in the group switched to anastrozole therapy compared with the group who continued tamoxifen (HR 0.59; 95% CI 0.42, 0.82; $P < 0.0018$) [14]. Thus this larger trial confirmed the findings of the ITA trial, with significant benefits associated with switching adjuvant therapy from tamoxifen to anastrozole after 2–3 years of tamoxifen.

The Intergroup Exemestane Study (IES)

The Intergroup exemestane study recruited 4,742 postmenopausal women with oestrogen receptor-positive or unknown receptor status tumours, of which 44% were node-positive. Patients were randomised to exemestane or continued tamoxifen after 2–3 years of adjuvant tamoxifen. Results were reported at a median follow-up of 31 months, with 183 events in the exemestane group and 266 events in the tamoxifen group [6]. As in the other trials, this study found that switching to exemestane significantly improved disease-free survival compared with continuing tamoxifen therapy (HR 0.68; 95% CI 0.56, 0.82; $P < 0.001$) (Fig. 3). Switching to exemestane was also associated with significant improvement of distant disease-free survival (HR 0.66; 95% CI 0.52, 0.83; $P = 0.0004$) and reduced risk of contralateral breast cancer (HR 0.44; 95% CI 0.20, 0.98; $P = 0.04$) compared with continued tamoxifen.

As with the primary adjuvant trials, this study indicates that 5 years of primary adjuvant tamoxifen therapy is not optimal for postmenopausal women with hormone receptor-positive EBC. For patients who have



CI, confidence intervals; HR, hazard ratio

Fig. 3 Kaplan–Meier probability of disease-free survival in the International Exemestane Study (IES) at a median follow-up of 31 months [6]. Copyright 2004 Massachusetts Medical Society. All rights reserved

already received 2–3 years of adjuvant tamoxifen, clinicians should consider switching to an AI such as anastrozole or exemestane.

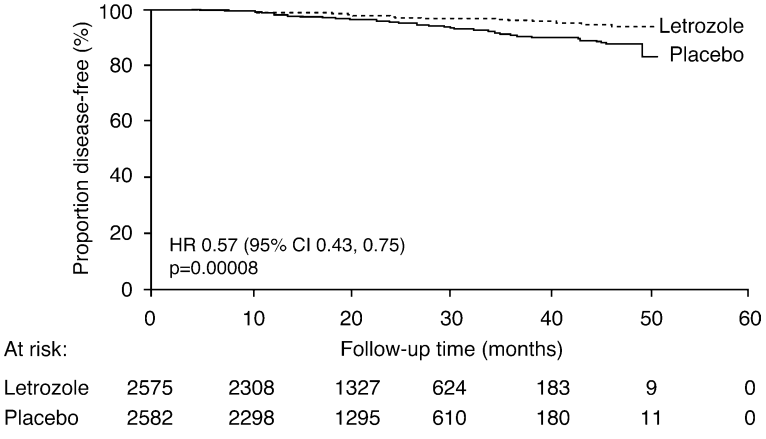
Extended adjuvant therapy for women who have completed 5 years of tamoxifen

The MA 17 trial randomised 5,187 postmenopausal women who had completed approximately 5 (4.5–6) years of adjuvant tamoxifen to letrozole or placebo for a further 5 years. The first interim analysis occurred at a median follow-up of 29 months, with 75 events in the letrozole group and 132 events in the placebo group. The results, showing that letrozole significantly prolonged disease-free survival compared with placebo (HR 0.57; 95% CI 0.43, 0.75; $P = 0.00008$) (Fig. 4) [13], led to early closure of the study. The final analysis was presented at ASCO 2004 at a median follow-up of 30 months and showed that while there was no significant difference in overall survival in the total population ($P = 0.30$) and in node-negative patients (50% of total population; HR 1.52; 95% CI 0.76, 3.06; $P = 0.24$), there was a significant difference in node-positive patients (46% of total population; HR 0.61; 95% CI 0.38, 0.98; $P = 0.04$) [12].

The results of the MA 17 trial indicate that letrozole should be considered for patients who have completed 5 years of tamoxifen [13]. However, the optimal duration of treatment is not known, and the lack of long-term efficacy and safety data means that an overall risk:benefit assessment cannot be made. As more women receive an AI within the first 5 years, a diminishing proportion of patients are likely to complete 5 years of adjuvant tamoxifen.

What is the most effective strategy: primary adjuvant therapy with an aromatase inhibitor or initial tamoxifen followed by an aromatase inhibitor?

The mature results of the ATAC trial have shown that anastrozole has significant efficacy and tolerability benefits and a favourable therapeutic index compared with tamoxifen, when used as primary adjuvant therapy for postmenopausal women with EBC. The switching trials have also shown that AI therapy with anastrozole or exemestane after 2–3 years of tamoxifen significantly improves disease-free survival compared with the standard 5 years of tamoxifen treatment. Furthermore, after 5 years of tamoxifen, extended adjuvant treatment with



CI, confidence intervals; HR, hazard ratio

Fig. 4 Kaplan–Meier probability of disease-free survival in the MA.17 trial at a median follow-up of 29 months [13]. Copyright 2003, Massachusetts Medical Society. All rights reserved

letrozole significantly improves disease-free survival compared with placebo.

No sequencing data are yet available so it is not possible definitively to determine whether primary adjuvant therapy with AI or initial tamoxifen followed by an AI is the most effective strategy. The results from the primary and switching studies cannot be directly compared since they are of different design and include different patient populations (e.g. switching and extended adjuvant trials enrol preselected patient populations of responders to endocrine therapy, since patients with recurrences or adverse events that occur before randomisation during the adjuvant therapy period are not included). However, we can reach some conclusions based on our knowledge of the progression of breast cancer and the clinical trial data available.

The primary aim of breast cancer therapy is to minimise the risk of recurrences, the majority of which occur during the first 5 years post-surgery, with a peak at 1–2 years [7, 15]. Both anastrozole and letrozole have been shown to lower the risk of recurrence within the first 2–3 years of adjuvant therapy compared with tamoxifen [1, 4]. Also, more patients who are treated with tamoxifen withdraw from treatment during the first 2–3 years compared with those who receive anastrozole therapy [1]. These findings suggest that to prevent disease recurrence and improve life expectancy in postmenopausal women with EBC the most effective adjuvant therapy should be used first. As anastrozole is the only AI with mature primary adjuvant data today; the available evidence suggests that anastrozole should be the adjuvant treatment of choice over tamoxifen.

Conclusions

These trials indicate that tamoxifen is no longer the most appropriate initial choice for adjuvant therapy in postmenopausal women with hormone-sensitive EBC, and that better options exist for women already receiving adjuvant tamoxifen. This conclusion has been recognised in the most recent Technology Assessment from ASCO [16], which recommends that adjuvant endocrine therapy for postmenopausal women with hormone-sensitive EBC should include an AI either initially or after 2–3 or 5 years of tamoxifen to lower the risk of tumour recurrence. Currently, anastrozole is the only AI licensed as alternative adjuvant therapy to tamoxifen, and has the most mature safety data in this setting.

References

1. ATAC Trialists' Group (2002) 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 359:2131–2139
2. ATAC Trialists' Group (2003) Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early stage breast cancer. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial efficacy and safety update analyses. Cancer 98:1802–1810
3. ATAC Trialists' Group (2005) Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 365:60–62
4. BIG 1-98 Collaborative Group (2005) BIG 1-98: a prospective randomized double-blind double-dummy phase III study to evaluate letrozole as adjuvant endocrine therapy for postmenopausal women with receptor-positive breast cancer. Breast 14:S3
5. Boccardo F, Rubagotti A, Guglielmini P, Amoroso D, Fini A, Paladini G, Mesiti M, Romeo D, Rinaldini M, Scali S, Porpiglia M, Benedetto C (2005) Switching to anastrozole versus continued tamoxifen treatment of early breast cancer. Preliminary results of the Italian Tamoxifen Anastrozole (ITA) trial. J Clin Oncol 23:5138–5147
6. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, Jones SE, Alvarez I, Bertelli G, Ortmann O, Coates AS, Bajetta E, Dodwell D, Coleman RE, Fallowfield LJ, Mickiewicz E, Andersen J, Lonning PE, Cocconi G, Stewart A, Stuart N, Snowdon CF, Carpentieri M, Massimini G, Bliss JM (2004) Intergroup Exemestane Study. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 350:1081–1092
7. Early Breast Cancer Trialists' Collaborative Group (1998) Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 352:930–942
8. Early Breast Cancer Trialists' Collaborative Group (1998) Tamoxifen for early breast cancer: an overview of the randomised trials. Lancet 351:1451–1467
9. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, Costantino J, Redmond C, Fisher ER, Bowman DM, Deschenes L, Dimitrov NV, Margolese RG, Robidoux A, Shibata H, Terz J, Paterson AH, Feldman MI, Farrar W, Evans J, Lickely H (1996) 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 88:1529–1542
10. Fisher B, Dignam J, Bryant J, Wolmark N (2001) Five versus more than five years of tamoxifen for lymph node-negative breast cancer: updated findings from the National Surgical Adjuvant Breast and Bowel Project B-14 randomized trial. J Natl Cancer Inst 93:684–690
11. Fisher B, Jeong JH, Dignam J, Anderson S, Mamounas E, Wickerham DL, Wolmark N (2001) Findings from recent National Surgical Adjuvant Breast and Bowel Project adjuvant studies in stage I breast cancer. J Natl Cancer Inst Monogr 30:62–66
12. Goss PE (2004) NCIC CTG MA.17 final analysis of updated data: a placebo-controlled trial of letrozole following tamoxifen as adjuvant therapy in postmenopausal women with early breast cancer. Available at http://www.asco.org/ac/1,1003,_12-002511-00_18-0026-00_19-0011301,00.asp. Accessed 10 Nov 2004.
13. Goss PE, Ingle JN, Martino S, Robert NJ, Muss HB, Piccart MJ, Castiglione M, Tu D, Shepherd LE, Pritchard KI, Livingston RB, Davidson NE, Norton L, Perez EA, Abrams JS, Therasse P, Palmer MJ, Pater JL (2003) A randomized trial of letrozole in postmenopausal women after five years of tamoxifen therapy for early stage breast cancer. N Engl J Med 349:1793–1802
14. Jakesz R, Kaufmann M, Gnant M, Jonat W, Mittleboek M, Greil R, Tausch C, Hilfrich J, Kwasny W, Samonigg H, on behalf of the ABCSG and the GABG (2004) Benefits of switching postmenopausal women with hormone-sensitive early breast cancer to anastrozole after 2 years adjuvant tamoxifen: combined results from 3,123 women enrolled in the ABCSG Trial 8 and the ARNO 95 Trial (abstract 2). Breast Cancer Res Treat 88:S7

15. Saphner T, Tormey DC, Gray R (1996) Annual hazard rates of recurrence for breast cancer after primary therapy. J Clin Oncol 14:2738–2746
16. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, Chlebowski RT, Gelber R, Edge SB, Gralow J, Cobleigh MA, Mamounas EP, Goldstein LJ, Whelan TJ, Powles TJ, Bryant J, Perkins C, Perotti J, Braun S, Langer AS, Perotti J, Powles TJ, Whelan TJ, Browman GP (2005) 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 23:619–629