

Practical consensus recommendations on duration of adjuvant hormonal therapy in breast cancer

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Abstract

Optimization of adjuvant systemic therapy in women with early-stage hormone receptor-positive breast cancer includes the consideration of chemotherapy and duration of hormone therapy. Adjuvant hormonal therapy significantly improves long-term survival of breast cancer patients with hormone receptor-positive disease. Despite the proven clinical efficacy of tamoxifen and aromatase inhibitors, many breast cancer survivors either fail to take the correct dosage at the prescribed frequency (adherence) or discontinue therapy (persistence). Expert oncologist discussed on the duration of adjuvant hormonal therapy for improvement of OS and quality of life of breast cancer patients by providing reduction in recurrence and mortality. This expert group used data from published literature, practical experience and opinion of a large group of academic oncologists to arrive at this practical consensus recommendations for the benefit of community oncologists.

Key words: Anastrozole, axillary node, long term therapy, zoledronic acid

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]

Adjuvant hormonal therapy for hormone-sensitive breast cancer has been one of the most important additions to the treatment of breast cancer, resulting in impressive reductions in the breast cancer recurrence and mortality rates.^[2,3] These oral therapies include either tamoxifen and/or an aromatase inhibitor and are typically prescribed for 5 years or longer. Surprisingly, despite the dramatic efficacy of hormonal agents, there is increasing evidence that the early discontinuation and non-adherence rates for both tamoxifen and aromatase inhibitors are high and often unrecognized.^[4-11]

Expert group of oncologist meet in the update in oncology-X-2017 to discuss on available strategies and duration of adjuvant hormonal therapy in treatment of breast cancer.

The update in oncology-X-2017 was organized by Sir Ganga Ram Hospital group met to discuss and arrive at a consensus statement to provide community oncologists practical guidelines for challenging common case scenarios in Breast Cancer out of these we are discuss about duration of adjuvant hormonal therapy in breast cancer in this chapter.

While the discussions will take the scenario as exists in India as a representative country with limited resources, the final manuscript is applicable globally.^[12,13] The discussion was based on domain expertise of the National as well as international faculty, published evidence and practical experience in real life management of breast cancer patients. Opinion of the 250 oncologist including medical oncologist, radiation oncologist, surgical oncologist, molecular oncologist and radiologist are present in the update in oncology-X-2017 was taken into consideration by the expert panel. The expert group was chaired by Dr. J B Sharma whereas the discussions were moderated by Dr. Sudeep Gupta and Dr. Manisha Singh. The core expert group Dr. Amish Vora, Dr. Govind K Babu, Dr. Meenu Walia, Dr. Stephen C Malamud, Dr. Vipul Nautial, Dr. Rajat Saha and Dr. B K Smruti. Consensus answers were used as the basis of formulating the consensus statement providing community oncologists with ready-to-use practical recommendations. The survey answers were used as the basis for formulating the consensus statement so that community oncologists have a ready-to-use duration of adjuvant hormonal therapy in treatment of breast cancer.

As part of the background work, the best existing evidence was compiled and provided to the expert group panel members for review in preparation of the expert group meeting.^[14-16] The national and international experts invited to this meeting were also provided the data on the voting by the audience delegates from the update in oncology-X-2017. Members of the panel were also allowed to share their personal experiences, make comments and record dissent while voting for the consensus statements. Total of Three broad question categories were part of the expert group discussions [Tables 1-4].

Oncology has made notable strides in the development of effective treatments to improve cancer survival. It is, therefore, surprising that adherence appears to be almost as significant a problem in oncology for these potentially life-saving medications, such as chemotherapy, as for other diseases.^[17-23]

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Table 1: Question categories addressed by the update in oncology-X-2017**Broad question title**

Case 1-60 years postmenopausal lady diagnosed with infiltrating duct carcinoma left breast. She undergoes modified radical mastectomy. HPE results - T2N0M0. ER positive, PR positive, HER 2/neu negative. Cannot afford oncotype Dx. She takes adjuvant chemotherapy followed by hormonal therapy with anastrozole for 5 years

Question 1 - What will you do next?

Question 2 - If the patient is single node positive. What will you do?

Question 3 - If the patient is multiple nodes positive. What will you do?

Update in oncology-X-2017

ER=Estrogen receptor, PR=Progesterone receptor, HER 2=Human epidermal growth factor receptor 2

Table 2: Question 1 - What will you do next?

Options (%)	Anastrozole and add zoledronic acid	Switch to tamoxifen	Stop anastrozole and do nothing
Percentage of polled oncologists	25	50	25

Expert group consensus: Continue anastrozole and add zoledronic acid

Table 3: Question 2 - If the patient is single node positive. What will you do?

Options (%)	Continue anastrozole	Stop anastrozole	No further endocrine therapy
Percentage of polled oncologists	50	33.3	16.7

Expert group consensus: Continue anastrozole

Table 4: Question 3 - If the patient is multiple nodes positive. What will you do?

Options (%)	Continue anastrozole	Stop anastrozole
Percentage of polled oncologists	75	25

Expert group consensus: Continue anastrozole

One of the most dramatic and important additions to the treatment of breast cancer has been adjuvant hormonal therapy for hormone-sensitive breast cancer, with impressive reductions in recurrence and mortality.^[24,25] These oral agents include tamoxifen and aromatase inhibitors (AIs) and are typically prescribed for 5 years or longer. Nonetheless, it is surprising to find that, despite the dramatic efficacy of hormonal agents, there is a discontinuation rate of approximately 7% to 10% per year for tamoxifen and AIs.^[26-33] Reports indicate that only 40% to 60% of patients with BC finish their recommended courses of hormonal therapy, despite the fact that randomized trials show higher recurrence rates and worse survival with \geq 5 years of treatment.^[32,34-37]

Adjuvant medical therapy for patients with primary breast cancer has led to a substantial reduction in mortality from this disease.^[38] However, adjuvant therapy trials to test the many new agents that are in development would require thousands of patients, many years of follow-up and very large resources. In the absence of such trial data, there is an urgent need for biomarkers of efficacy that can reliably predict long-term outcomes. Endocrine treatments for breast cancer appear to act largely by inhibiting tumor cell proliferation. Thus, markers of

tumor cell proliferation, such as Ki67, are candidate markers of efficacy that can be evaluated after short-term (e.g., 2 weeks) treatment of primary breast cancer patients, before they undergo surgery.

Tamoxifen is a selective estrogen receptor (ER) modulator that acts (along with its metabolites) largely or wholly by competitive binding to the receptor protein.^[39] In the 75% to 80% of patients with early breast cancer who have ER-positive disease, treatment with 5 years of tamoxifen immediately and substantially reduces local, contralateral, and distant recurrence rates and reduces 15-year breast cancer mortality, with little effect on the aggregate of all other causes of death.^[40,41] However, there is little or no effect on breast cancer outcomes in ER-negative disease. The early results from the first clinical trials of tamoxifen showed only a small absolute gain in 5-year survival, 3 but the additional mortality reductions during years 5 to 9 and 10 to 14 were each about as great as the mortality reduction during years 0 to 4 (the 5 years while tamoxifen was still being taken).^[40] Hence, the absolute reduction in breast cancer mortality produced by 5 years of tamoxifen was almost three times as great 15 years after diagnosis as it had been only 5 years after diagnosis.

For more than 20 years, the anti-oestrogen tamoxifen has been the established endocrine adjuvant therapy after surgery for postmenopausal women with early breast cancer. 5 years is generally judged the optimum duration for treatment,^[41] since tamoxifen therapy beyond 5 years seems to confer no extra benefit in terms of disease-free survival.^[42,43] However, several side effects are inherent with long-term tamoxifen treatment. The partial oestrogenic activity of tamoxifen in some tissues leads to an increased risk of endometrial cancer and thromboembolic events over the course of treatment.^[44-46] Tamoxifen resistance can also develop.^[47]

The 5-year standard for adjuvant tamoxifen therapy, therefore, seems to be imposed by the limitations of the drug rather than by the optimum duration of therapy. In particular, the relapse pattern for low-risk and intermediate-risk tumours indicates that adjuvant treatment should continue after 5 years, with overview results suggesting that there is a 1.5–2% yearly risk of recurrence of breast cancer in years 5–15 after initial diagnosis.^[48,49] The 15-year outcome of some oestrogen-receptor positive tumours might be worse than that of oestrogen receptor negative lesions.^[50] The administration of tamoxifen beyond the optimum time of efficacy might, therefore, result in side-effects without a concomitant therapeutic benefit.

The limitations of tamoxifen have led to a search for alternative endocrine therapies with increased efficacy and fewer long-term complications. The third-generation aromatase inhibitors anastrozole, letrozole, and exemestane are highly selective for aromatase and inhibit 97–99% of oestrogen synthesis from this source.^[51,52] Results of trials such as the ATAC study^[53] have shown the improved efficacy and tolerability of anastrozole over tamoxifen, and data now support the use of 5 years' anastrozole as adjuvant therapy for postmenopausal women with early breast cancer. However, tamoxifen is still a useful and ubiquitous treatment option, and by employing a strategy of switching therapy from tamoxifen to an aromatase inhibitor, the unnecessary longer-term side-effects of tamoxifen might be

obviated and the complications of long-term tamoxifen therapy avoided. Data indicate a positive effect on recurrence-free survival when switching from tamoxifen to an aromatase inhibitor.^[54,55]

The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial,^[56] 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^[57-59] have shown the benefits of switching to anastrozole compared with remaining on tamoxifen for 5 years. The results of the combined analysis^[59] 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^[57,58] also showed significant clinical benefits from switching to anastrozole after 2–3 years of adjuvant tamoxifen. The most recent technical assessment from the American Society of Clinical Oncology (ASCO)^[60] recommends that optimum adjuvant therapy for postmenopausal women should now include the use of an aromatase inhibitor, either as initial treatment or after 2–5 years' treatment with tamoxifen, to reduce the risk of tumour recurrence. Clearly, third-generation aromatase inhibitors have a key role in management of postmenopausal women with early stage breast cancer, 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.^[60]

The ASCO assessment favours using the aromatase inhibitor that has been most studied in the setting closest to the individual patient's clinical circumstance.

Conclusion

In conclusion of this discussion switching treatment to an aromatase inhibitor offers the opportunity to continue adjuvant hormonal therapy for longer than 5 years, since problems of tolerability that arise from the partial agonist effects of tamoxifen are circumvented. As per ASCO guidelines recommended treatment of women who have hormone receptor–positive breast cancer and are premenopausal with 5 years of tamoxifen, and those who are postmenopausal a minimum of 5 years of adjuvant therapy with an aromatase inhibitor or tamoxifen followed by an aromatase inhibitor (in sequence). If women are pre-or perimenopausal and have received 5 years of adjuvant tamoxifen, they should be offered 10 years total duration of tamoxifen. If women are postmenopausal and have received 5 years of adjuvant tamoxifen, they should be offered the choice of continuing tamoxifen or switching to an aromatase inhibitor for 10 years total adjuvant endocrine therapy. The optimal timing and duration of endocrine treatment remain unresolved.

Take Home Message

Case - 60 year postmenopausal lady diagnosed with infiltrating duct carcinoma left breast. She undergoes modified radical mastectomy. HPE results - T2N0M0. ER++ve, PR+ve, Her2/Neu-ve. Not willing for Oncotype Dx. She has taken adjuvant chemotherapy followed by hormonal therapy with anastrozole for five years. Now she comes for follow up, is asymptomatic and asks what she should do next

- 1 Continue anastrozole and add zoledronic acid
- 2 Continue anastrozole if original disease was single axillary node positive
- 3 The recommendation remains the same even if the original disease was with multiple axillary lymph node positivity.

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Conflicts of interest

There are no conflicts of interest.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74-108.
2. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, *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.
3. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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.
4. Kimmick G, Anderson R, Camacho F, Bhosle M, Hwang W, Balkrishnan R, *et al.* Adjuvant hormonal therapy use among insured, low-income women with breast cancer. *J Clin Oncol* 2009;27:3445-51.
5. Ziller V, Kalder M, Albert US, Holzhauser W, Ziller M, Wagner U, *et al.* Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. *Ann Oncol* 2009;20:431-6.
6. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A, *et al.* Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol* 2008;26:556-62.
7. Chlebowski RT, Geller ML. Adherence to endocrine therapy for breast cancer. *Oncology* 2006;71:1-9.
8. Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA. Adherence to tamoxifen over the five-year course. *Breast Cancer Res Treat* 2006;99:215-20.
9. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst* 2002;94:652-61.
10. McCowan C, Shearer J, Donnan PT, Dewar JA, Crilly M, Thompson AM, *et al.* Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *Br J Cancer* 2008;99:1763-8.
11. Barron TI, Connolly R, Bennett K, Feely J, Kennedy MJ. Early discontinuation of tamoxifen: A lesson for oncologists. *Cancer* 2007;109:832-9.
12. National Cancer Registry Programme, Indian Council of Medical Research. Leading sites of cancer. In: Consolidated Report of Population Based Cancer Registries 2001-2004, Incidence and Distribution of Cancer. Bangalore: Coordinating Unit, National Cancer Registry Programme (ICMR); 2006. p. 8-30.
13. Badwe RA, Gangawal S, Mittra I, Desai PB. Clinico-pathological features and prognosis of breast cancer in different religious communities in India. *Indian J Cancer* 1990;27:220-8.
14. Altekruse SF, Kosary CL, Krapcho M, editors. SEER Cancer Statistics Review. National Cancer Institute; 19752007.
15. National Cancer Registry Program. Ten Year Consolidated Report of the Hospital Based Cancer Registries, 1984–1993, an Assessment of the Burden and Care of Cancer Patients. New Delhi: Indian Council of Medical Research; 2001.
16. Agarwal G, Pradeep PV, Aggarwal V, Yip CH, Cheung PS. Spectrum of breast cancer in Asian women. *World J Surg* 2007;31:1031-40.
17. Magai C, Considine N, Neugut AI, Hershtman DL. Common psychosocial factors underlying breast cancer screening and breast cancer South Asian Journal of Cancer ♦ Volume 7 ♦ Issue 2 ♦ April-June 2018

- treatment adherence: A conceptual review and synthesis. *J Womens Health (Larchmt)* 2007;16:11-23.
18. Magai C, Consedine NS, Adjei BA, Hershman D, Neugut A. Psychosocial influences on suboptimal adjuvant breast cancer treatment adherence among African American women: Implications for education and intervention. *Health Educ Behav* 2008;35:835-54.
 19. Escalada P, Griffiths P. Do people with cancer comply with oral chemotherapy treatments? *Br J Community Nurs* 2006;11:532-6.
 20. Hershman D, McBride R, Jacobson JS, Lamerato L, Roberts K, Grann VR, *et al.* Racial disparities in treatment and survival among women with early-stage breast cancer. *J Clin Oncol* 2005;23:6639-46.
 21. Neugut AI, Matasar M, Wang X, McBride R, Jacobson JS, Tsai WY, *et al.* Duration of adjuvant chemotherapy for colon cancer and survival among the elderly. *J Clin Oncol* 2006;24:2368-75.
 22. Dobie SA, Baldwin LM, Dominitz JA, Matthews B, Billingsley K, Barlow W, *et al.* Completion of therapy by medicare patients with stage III colon cancer. *J Natl Cancer Inst* 2006;98:610-9.
 23. Morris M, Platell C, Fritschi L, Iacopetta B. Failure to complete adjuvant chemotherapy is associated with adverse survival in stage III colon cancer patients. *Br J Cancer* 2007;96:701-7.
 24. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, *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.
 25. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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.
 26. Kimnick G, Anderson R, Camacho F, Bhosle M, Hwang W, Balkrishnan R, *et al.* Adjuvant hormonal therapy use among insured, low-income women with breast cancer. *J Clin Oncol* 2009;27:3445-51.
 27. Ziller V, Kalder M, Albert US, Holzhauer W, Ziller M, Wagner U, *et al.* Adherence to adjuvant endocrine therapy in postmenopausal women with breast cancer. *Ann Oncol* 2009;20:431-6.
 28. Partridge AH, LaFountain A, Mayer E, Taylor BS, Winer E, Asnis-Alibozek A, *et al.* Adherence to initial adjuvant anastrozole therapy among women with early-stage breast cancer. *J Clin Oncol* 2008;26:556-62.
 29. Chlebowski RT, Geller ML. Adherence to endocrine therapy for breast cancer. *Oncology* 2006;71:1-9.
 30. Lash TL, Fox MP, Westrup JL, Fink AK, Silliman RA. Adherence to tamoxifen over the five-year course. *Breast Cancer Res Treat* 2006;99:215-20.
 31. Partridge AH, Avorn J, Wang PS, Winer EP. Adherence to therapy with oral antineoplastic agents. *J Natl Cancer Inst* 2002;94:652-61.
 32. McCowan C, Shearer J, Donnan PT, Dewar JA, Crilly M, Thompson AM, *et al.* Cohort study examining tamoxifen adherence and its relationship to mortality in women with breast cancer. *Br J Cancer* 2008;99:1763-8.
 33. Barron TI, Connolly R, Bennett K, Feely J, Kennedy MJ. Early discontinuation of tamoxifen: A lesson for oncologists. *Cancer* 2007;109:832-9.
 34. Randomized trial of two versus five years of adjuvant tamoxifen for postmenopausal early stage breast cancer. Swedish Breast Cancer Cooperative Group. *J Natl Cancer Inst* 1996;88:1543-9.
 35. Geiger AM, Thwin SS, Lash TL, Buist DS, Prout MN, Wei F, *et al.* Recurrences and second primary breast cancers in older women with initial early-stage disease. *Cancer* 2007;109:966-74.
 36. Yood MU, Owusu C, Buist DS, Geiger AM, Field TS, Thwin SS, *et al.* Mortality impact of less-than-standard therapy in older breast cancer patients. *J Am Coll Surg* 2008;206:66-75.
 37. Bryant J, Fisher B, Dignam J. Duration of adjuvant tamoxifen therapy. *J Natl Cancer Inst Monogr* 2001;56-61.
 38. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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.
 39. Jordan VC. The science of selective estrogen receptor modulators: Concept to clinical practice. *Clin Cancer Res* 2006;12:5010-3.
 40. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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.
 41. Goldhirsch A, Wood WC, Gelber RD, Coates AS, Thürlimann B, Senn HJ, *et al.* Meeting highlights: Updated international expert consensus on the primary therapy of early breast cancer. *J Clin Oncol* 2003;21:3357-65.
 42. Peto R. Five years of tamoxifen – or more? *J Natl Cancer Inst* 1996;88:1791-3.
 43. Fisher B, Dignam J, Bryant J, DeCillis A, Wickerham DL, Wolmark N, *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.
 44. Early Breast Cancer Trialists' Collaborative Group (EBCTCG). 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.
 45. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM, *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.
 46. Jaiyesimi IA, Buzdar AU, Decker DA, Hortobagyi GN. Use of tamoxifen for breast cancer: Twenty-eight years later. *J Clin Oncol* 1995;13:513-29.
 47. Clarke R, Leonessa F, Welch JN, Skaar TC. Cellular and molecular pharmacology of antiestrogen action and resistance. *Pharmacol Rev* 2001;53:25-71.
 48. Early Breast Cancer Trialists' Collaborative Group. Tamoxifen for early breast cancer. (Cochrane Review). In: *The Cochrane Library*. Chichester: John Wiley and Sons; 2004.
 49. Saphner T, Tormey DC, Gray R. Annual hazard rates of recurrence for breast cancer after primary therapy. *J Clin Oncol* 1996;14:2738-46.
 50. Morandi P, Middleton LP, Mirza NQ. Occult breast cancer (OBC), a retrospective analysis of clinico-pathological characteristics and long-term outcome: the University of Texas MD Anderson Cancer Center experience. *Breast Cancer Res Treat* 2004;88:S165.
 51. Geisler J, King N, Anker G, Ornati G, Di Salle E, Lønning PE, *et al.* *In vivo* inhibition of aromatization by exemestane, a novel irreversible aromatase inhibitor, in postmenopausal breast cancer patients. *Clin Cancer Res* 1998;4:2089-93.
 52. Geisler J, Haynes B, Anker G, Dowsett M, Lønning PE. Influence of letrozole and anastrozole on total body aromatization and plasma estrogen levels in postmenopausal breast cancer patients evaluated in a randomized, cross-over study. *J Clin Oncol* 2002;20:751-7.
 53. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, *et al.* Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60-2.
 54. Boccardo F, Rubagotti A, Puntoni M, Guglielmini P, Amoroso D, Fini A, *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.
 55. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, *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.
 56. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, *et al.* Results of the ATAC (Arimidex, tamoxifen, alone or in combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 2005;365:60-2.
 57. Boccardo F, Rubagotti A, Puntoni M, Guglielmini P, Amoroso D, Fini A, *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.
 58. Boccardo F, Rubagotti A, Puntoni M; 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.
 59. Jakesz R, Jonat W, Gnani M, Mittlboeck M, Greil R, Tausch C, *et al.* 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.
 60. Winer EP, Hudis C, Burstein HJ, Wolff AC, Pritchard KI, Ingle JN, *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.