



RECOMMENDATIONS FOR USE OF

Endocrine therapy

for the treatment of hormone receptor-positive advanced breast cancer

A CLINICAL PRACTICE GUIDELINE DEVELOPED BY NATIONAL BREAST AND OVARIAN CANCER CENTRE (NBOCC)

This document supplements guideline recommendations 22, 24a and 24b about the use of endocrine therapy in National Breast Cancer Centre* *Clinical practice guidelines for the management of advanced breast cancer*, 2nd edition, 2001 (page 9).¹

PURPOSE

This guideline includes statements and recommendations based on available, high level evidence about the use of endocrine therapy for pre-menopausal and post-menopausal women with hormone receptor-positive advanced breast cancer. The guideline aims to provide health professionals with information to assist in making management recommendations for improved patient outcomes. National Breast and Ovarian Cancer Centre (NBOCC) also develops information specifically for consumers about advanced breast cancer diagnosis and treatment options.

For information on the Pharmaceutical Benefits Scheme (PBS) listing for drugs mentioned in the guideline please see page 19 of this guideline.

Endorsed by:



Faculty of
Radiation Oncology



The Royal Australasian
College of Physicians



The Royal Australasian
College of Surgeons

BACKGROUND

Endocrine therapy is a type of treatment, that acts to inhibit the growth of breast cancer cells which have hormone receptors. It does this by blocking either the production of female hormones or the ability of hormones to interact with receptors on cancer cells.

Endocrine therapies include:

- ovarian suppression/ablation, e.g. luteinising hormone-releasing hormone agonists (goserelin, buserelin), ovarian irradiation, and surgical oophorectomy
- selective oestrogen receptor modulators, e.g. tamoxifen
- selective oestrogen receptor downregulators, e.g. fulvestrant
- progestins, e.g. megestrol acetate and medroxyprogesterone
- aromatase inhibitors, e.g. anastrozole, exemestane, letrozole.

This guideline is based on a meta-analysis² and an evidence review.³ The meta-analysis is about the use of endocrine therapy in pre-menopausal women with hormone receptor-positive advanced breast cancer. The evidence review is about the use of endocrine therapy in post-menopausal women with hormone receptor-positive advanced breast cancer. The evidence is not specific to women with metastatic (stage IV) breast cancer. While the majority of women had stage IV metastatic disease, a small number of women with locally advanced disease and/or locoregional recurrence were included in the trials. In the majority of trials, women with tumours of unknown hormone receptor status were also eligible for participation.

A previous Cochrane review (2003)⁴ investigating randomised trials comparing the effects of chemotherapy alone with endocrine therapy alone in women with metastatic breast cancer found that endocrine therapy is the preferred first-line treatment for women with hormone receptor-positive breast cancer, except in the presence of rapidly progressive disease. The review also found that the incidence of adverse events is less frequent with endocrine therapy compared with chemotherapy.

SUMMARY OF EVIDENCE

Use of endocrine therapy for pre-menopausal women with hormone receptor-positive advanced breast cancer

The statements and recommendations about pre-menopausal women are based on evidence from a meta-analysis² of four randomised trials. The trials compared the use of luteinising hormone-releasing hormone (LH-RH) agonist alone compared with the use of LH-RH agonist plus tamoxifen in pre-menopausal women with advanced breast cancer.

Combined therapy of LH-RH agonist plus tamoxifen significantly improved overall survival and progression-free survival compared with LH-RH agonist alone in pre-menopausal women with advanced breast cancer. Another trial⁵ found a significant improvement in survival outcomes for women treated with combined LH-RH agonist plus tamoxifen compared with tamoxifen alone. This trial also found a significantly reduced incidence of hot flushes in women treated with tamoxifen alone.

All trials investigating the use of endocrine therapy in pre-menopausal women used a LH-RH agonist. Although not formally compared in a trial setting, it is reasonable to assume that all forms of ovarian ablation or ovarian functional suppression are equivalent and have similar effects.

Use of endocrine therapy for post-menopausal women with hormone receptor-positive advanced breast cancer

The statements and recommendations about post-menopausal women are based on evidence from 14 randomised trials assessing the use of endocrine therapy for post-menopausal women with hormone receptor-positive advanced breast cancer:

- five trials compared a third generation aromatase inhibitor with tamoxifen as first-line therapy⁶⁻¹⁰
- five trials compared a third generation aromatase inhibitor with progestins (megestrol acetate) as second-line therapy¹¹⁻¹⁵
- two trials compared a third generation aromatase inhibitor with fulvestrant as second-line therapy^{16,17}
- two trials compared one third generation aromatase inhibitors with another.^{18,19}

(see table I on page 11 for trial details)

As first-line therapy, aromatase inhibitors significantly improved progression-free survival and overall response rate compared with tamoxifen in post-menopausal women with hormone receptor-positive advanced breast cancer. Improvements in overall survival have not been demonstrated. Overall, there was no significant difference in total adverse events between aromatase inhibitors and tamoxifen, although the incidence of vaginal bleeding and thromboembolic events was significantly lower in women treated with aromatase inhibitors. One study reported that quality of life was comparable for aromatase inhibitors and tamoxifen.³

As second-line therapy, aromatase inhibitors significantly improved progression-free survival and overall survival for women compared with progestins. Overall, both treatments were well tolerated. Patients treated with aromatase inhibitors experienced significantly higher incidence of nausea, hot flushes, and diarrhoea but a significantly lower incidence of dyspnoea compared with patients treated with progestins. Where reported, quality of life data comparing aromatase inhibitors and progestins are conflicting and no firm conclusions can be drawn. There were no significant differences in efficacy or safety with the use of aromatase inhibitors compared with fulvestrant.³

Of the two trials that compared one aromatase inhibitor with another, treatment was administered first-line in one trial¹⁸ and second-line in the other.¹⁹ Superiority of one aromatase inhibitor over another is yet to be determined.

* In February 2008, National Breast Cancer Centre incorporating the Ovarian Cancer Program (NBCC) changed its name to National Breast and Ovarian Cancer Centre (NBOCC)

STATEMENTS AND RECOMMENDATIONS

STATEMENTS	LEVEL OF EVIDENCE ²⁰	REFERENCE
In women with hormone receptor-positive advanced breast cancer:		
Endocrine therapy is preferred for women with hormone receptor-positive advanced breast cancer in preference to chemotherapy except in the presence of rapidly progressive visceral disease	I	Cochrane 2003 ⁴
Endocrine therapy shows no significant difference in overall survival compared with chemotherapy	I	Cochrane 2003 ⁴
Incidence of adverse events including nausea, vomiting and alopecia is less frequent with endocrine therapy compared with chemotherapy	I	Cochrane 2003 ⁴
In pre-menopausal women with hormone receptor-positive advanced breast cancer:		
Combination of luteinising hormone-releasing hormone (LH-RH) agonist and tamoxifen shows significant benefit in overall survival, progression-free survival and overall response rate compared with LH-RH agonist alone	I	Klijn 2001 ²
Combination of LH-RH agonist and tamoxifen shows significant benefit in overall survival, progression-free survival and overall response rate compared with tamoxifen alone	III	Klijn 2000 ⁵
Incidence of hot flushes is significantly higher in women treated with combined tamoxifen and LH-RH agonist compared with tamoxifen alone	III	Klijn 2000 ⁵
There are insufficient data to guide the use of third generation aromatase inhibitors in combination with functional ovarian ablation/suppression or fulvestrant in pre-menopausal women		

STATEMENTS	LEVEL OF EVIDENCE	REFERENCE
------------	-------------------	-----------

In post-menopausal women with hormone receptor-positive advanced breast cancer:

Combination of aromatase inhibitors and trastuzumab in women with HER2-positive hormone dependent advanced breast cancer leads to improved progression-free survival compared with aromatase inhibitors alone	II	NBCC ²¹
---	----	--------------------

First-line therapy

Third generation aromatase inhibitors ^a show no significant difference in overall survival compared with tamoxifen	I	NBOCC ³
---	---	--------------------

Third generation aromatase inhibitors ^b show significant benefit in progression-free survival compared with tamoxifen	I	NBOCC ³
--	---	--------------------

Third generation aromatase inhibitors ^c show significant benefit in overall response rate compared with tamoxifen	I	NBOCC ³
--	---	--------------------

Adverse events

Overall incidence of adverse events is not significantly different between third generation aromatase inhibitors and tamoxifen	I	NBOCC ³
--	---	--------------------

Incidence of thromboembolic events and vaginal bleeding is significantly lower with third generation aromatase inhibitors compared with tamoxifen	I	NBOCC ³
---	---	--------------------

Incidence of arthralgia, diarrhoea, dyspnoea, hot flushes, and nausea is not significantly different with third generation aromatase inhibitors compared with tamoxifen	I	NBOCC ³
---	---	--------------------

Quality of life

There are insufficient data to indicate any differences in quality of life between third generation aromatase inhibitors and tamoxifen		
--	--	--

^a Trials relate to anastrozole

^b Trials relate to anastrozole, letrozole

^c Trials relate to anastrozole, exemestane, letrozole

STATEMENTS	LEVEL OF EVIDENCE	REFERENCE
Second-line therapy (following progression on tamoxifen)		
Third generation aromatase inhibitors ^c show significant benefit in overall survival and progression-free survival compared with progestins ^d	I	NBOCC ³
Third generation aromatase inhibitors ^c show no significant difference in overall response rate compared with progestins	I	NBOCC ³
Third generation aromatase inhibitors show no significant difference in overall survival compared with fulvestrant ^a	II	NBOCC ³
Third generation aromatase inhibitors show no significant difference in progression-free survival and overall response rate compared with fulvestrant ^e	I	NBOCC ³
<i>Adverse events</i>		
Overall incidence of adverse events is not significantly different with third generation aromatase inhibitors compared with progestins	I	NBOCC ³
Incidence of dyspnoea is significantly lower with third generation aromatase inhibitors compared with progestins	I	NBOCC ³
Incidence of nausea, hot flushes and diarrhoea is significantly higher with third generation aromatase inhibitors compared with progestins	I	NBOCC ³
There are no significant differences in the incidence of thromboembolic events, vaginal bleeding and arthralgia between third generation aromatase inhibitors and progestins	I	NBOCC ³

STATEMENTS	LEVEL OF EVIDENCE	REFERENCE
<i>Quality of life</i>		
Where reported there is conflicting evidence about quality of life and no firm conclusions can be drawn	II	NBOCC ³

Aromatase inhibitor vs aromatase inhibitor

There are insufficient data to indicate a significant difference in overall survival, progression free survival or overall response rate for one aromatase inhibitor over another aromatase inhibitor^f

- a Trials relate to anastrozole
- c Trials relate to anastrozole, exemestane, letrozole
- d Trials relate to megestrol acetate
- e Trials relate to anastrozole and exemestane
- f For trial details please see table 1 on page 11

Recommendations to individuals should be based on the risks, the absolute benefits and harms of treatment, and their personal preference. These factors should be discussed with the woman. Women receiving endocrine therapy should be reviewed regularly and monitored for adverse events by clinicians familiar with endocrine therapy.

RECOMMENDATIONS	LEVEL OF EVIDENCE ²⁰	REFERENCE
In women with hormone receptor-positive advanced breast cancer:		
Endocrine therapy is recommended in preference to chemotherapy except in the presence of rapidly progressive visceral disease	I	Cochrane 2003 ⁴
Information about the treatment should be discussed with the patient. The patient should be adequately prepared for the treatment	I	NBCC & NCCI ²²
In pre-menopausal women with hormone receptor-positive advanced breast cancer:		
Tamoxifen combined with luteinising hormone-releasing hormone (LH-RH) agonist is recommended in favour of a LH-RH agonist alone	I	Klijn 2001 ²
If commencing treatment with tamoxifen alone, consideration should be given to adding a LH-RH agonist, if response is not optimal	III	Klijn 2000 ⁵
Optimal dose and schedule of administration		
Recommended doses and schedule are: Tamoxifen 20mg/day Goserelin 3.6mg subcutaneously monthly		Therapeutic Goods Administration ²³

RECOMMENDATIONS	LEVEL OF EVIDENCE	REFERENCE
In post-menopausal women with hormone receptor-positive advanced breast cancer:		
Aromatase inhibitors with trastuzumab are recommended for the treatment of women with HER2-positive hormone dependent advanced breast cancer in preference to aromatase inhibitors alone	II	NBCC ²¹
First-line treatment		
Third generation aromatase inhibitors are recommended in preference to tamoxifen	I	NBOCC ³
Second-line treatment <i>(following progression on tamoxifen)</i>		
Third generation aromatase inhibitors are recommended in preference to progestins	I	NBOCC ³
Optimal dose, schedule and duration of administration		
Continued use of third generation aromatase inhibitors is recommended until disease progression or unacceptable toxicity	I	NBOCC ³
Recommended doses and schedules for third generation aromatase inhibitors are: Anastrozole 1.0 mg/day Exemestane 25 mg/day Letrozole 2.5 mg/day	I	NBOCC ³
There are insufficient data to recommend one type of endocrine therapy over another for women who have progressed during or after treatment with adjuvant aromatase inhibitors		

SUMMARY OF TRIAL RESULTS

ENDOCRINE THERAPY IN PRE-MENOPAUSAL WOMEN

A meta-analysis of four trials² found that there was a significant overall survival benefit ($p=0.02$) and progression-free survival benefit ($p=0.0003$) for pre-menopausal women treated with combined tamoxifen and LH-RH agonist compared to pre-menopausal women treated with LH-RH agonist alone. One trial⁵ found that the incidence of hot flushes was significantly higher in women treated with combined tamoxifen and LH-RH agonist compared with women treated with tamoxifen alone (87% vs 40%; $p=0.0001$). There are currently insufficient data to guide the use of third generation aromatase inhibitors in combination with functional ovarian ablation/suppression or fulvestrant in pre-menopausal women. Further research is required to investigate the use of third generation aromatase inhibitors and fulvestrant in the pre-menopausal setting.

Overall survival

First-line therapy

A meta-analysis of two trials^{6,7} revealed third generation aromatase inhibitors confer no survival advantage over tamoxifen as first-line therapy for advanced breast cancer ($p=0.98$).

Second-line therapy

As second-line therapy a meta-analysis of four trials^{11-13,15} showed significant improvement in overall survival for women treated with third generation aromatase inhibitors compared with progestins ($p=0.003$). One trial showed a median survival benefit of 4.2 months.¹¹

ENDOCRINE THERAPY IN POST-MENOPAUSAL WOMEN

Table 1: Details of trials of endocrine therapy for post-menopausal women³

TRIAL	INTERVENTION	COMPARATOR	POSITION IN TREATMENT SEQUENCE
Aromatase inhibitor vs antioestrogen			
Bonnetterre 2001	Anastrozole 1.0 mg/day	Tamoxifen 20 mg/day	First-line for advanced disease
Milla-Santos 2003	Anastrozole 1.0 mg/day	Tamoxifen 40 mg/day	First-line for advanced disease
Paridaens 2003/4	Exemestane 25 mg/day	Tamoxifen 20 mg/day	First-line hormonal therapy for metastatic disease (≤ 1 CT regimen permitted)
Mouridsen 2001	Letrozole 2.5 mg/day	Tamoxifen 20 mg/day	First-line hormonal therapy for metastatic disease (≤ 1 CT regimen permitted)
Batra 2006	Letrozole 2.5 mg/day	Tamoxifen 20 mg/day	First-line for metastatic or recurrent disease
Mauriac 2003	Anastrozole 1.0 mg/day	Fulvestrant 250 mg/month IM	Second-line after endocrine therapy
Gradishar 2006	Exemestane 25 mg/day	Fulvestrant IM loading dose regimen ^a	Second-line after NSAI therapy
Aromatase inhibitor vs progestin			
Buzdar 1996 [North American and European trials]	Anastrozole 1.0 mg/day	Megestrol acetate 160 mg/day	Second-line after antioestrogen
Kaufmann 2000 [Trial EXE 018]	Exemestane 25 mg/day	Megestrol acetate 160 mg/day	Second-line after antioestrogen
Buzdar 2001	Letrozole 2.5 mg/day	Megestrol acetate 160 mg/day	Second-line after antioestrogen
Schmid 2001	Letrozole 2.5 mg/day	Megestrol acetate 160 mg/day	Possibly second-line ^b
Dombernowsky 1998	Letrozole 2.5 mg/day	Megestrol acetate 160 mg/day	Second-line after antioestrogen
Aromatase inhibitor vs aromatase inhibitor			
Mayordomo 2006 [GEICAM 2001-03]	Anastrozole 1.0 mg/day	Exemestane 25 mg/day	First-line hormonal for metastatic disease (previous CT permitted)
Rose 2003	Anastrozole 1.0 mg/day	Letrozole 2.5 mg/day	Second-line after antioestrogen

Notes: CT = chemotherapy; IM = intramuscular; NSAI = nonsteroidal aromatase inhibitor

^a 500 mg on Day 0, 250 mg on Days 14 and 28, and 250 mg every 28 days thereafter

^b Not explicitly stated in the publication

Progression-free survival

First-line therapy

A meta-analysis of two trials^{6,9} revealed that women treated with third generation aromatase inhibitors show significant advantage in progression-free survival ($p=0.0001$) compared with women treated with tamoxifen (Bonnetterre 2001:⁶ 8.5 vs 7 months, Mouridsen 2001:⁹ 9.4 vs 6 months).

Second-line therapy

A meta-analysis of four trials^{11-13,15} revealed a significant benefit in progression-free survival for women treated with third generation aromatase inhibitors compared to progestins ($p=0.01$).

A meta-analysis of two trials^{16,17} revealed no significant difference in progression-free survival between women treated with a third generation aromatase inhibitor compared with women treated with fulvestrant ($p=0.31$).

Overall response rate

First-line therapy

As first-line therapy a meta-analysis of four trials⁶⁻⁹ showed that third generation aromatase inhibitors are statistically superior to tamoxifen with respect to tumour response ($p=0.004$).

Second-line therapy

All five trials¹¹⁻¹⁵ in the meta-analysis found that overall response rate was higher in women treated with third generation aromatase inhibitors compared with women treated with progestins, although this difference was not significant. No trial has shown a statistically significant difference in overall response rate between women treated with third generation aromatase inhibitors compared with women treated with fulvestrant.

Comparing the efficacy of aromatase inhibitors

As first-line therapy, anastrozole and exemestane were not significantly different with respect to overall survival, progression-free survival, or overall response rate.

As second-line therapy, anastrozole and letrozole were equivalent in terms of overall survival and progression-free survival. Letrozole was statistically more effective than anastrozole in terms of overall response rate (19% vs 12%; $p=0.014$).¹⁹ This was not the case when women whose receptor status was unknown were excluded from the analysis.

Adverse events

First-line therapy

A meta-analysis^{6,7,9} of three trials showed no significant difference overall in adverse events between women treated with aromatase inhibitors compared with tamoxifen ($p=0.25$).

The largest trial in this meta-analysis (Bonnetterre)⁶ reported an overall incidence of adverse events with aromatase inhibitors of 83% compared with 85% for tamoxifen. However the incidence of vaginal bleeding was significantly lower in women treated with a third generation aromatase inhibitor compared with tamoxifen ($p<0.001$), as was the incidence of thromboembolic events ($p=0.003$).

Second-line therapy

There was no significant difference^{16,17} in overall incidence of adverse events between women treated with third generation aromatase inhibitors compared with women treated with fulvestrant (89% vs 89%; $p=0.79$). The incidence of specific adverse events (nausea, diarrhoea, rash, arthralgia, hot flashes, thromboembolic events and dyspnoea) was similar for both groups. The incidence of vaginal bleeding was not reported.

A meta-analysis of three trials^{12,13,15} showed no significant difference overall in adverse events for women treated with third generation aromatase inhibitors compared with progestins ($p=0.31$). There was however a significant increase of nausea ($p=0.005$), hot flashes ($p<0.001$), and diarrhoea ($p<0.001$) in women treated with a third generation aromatase inhibitor compared with women treated with a progestin. In contrast, the incidence of dyspnoea was significantly lower in women treated with aromatase inhibitors compared with progestins ($p<0.0001$).

Quality of life

Quality of life was poorly assessed and poorly reported across the trials and therefore no firm conclusions can be drawn. Most studies that did report on quality of life found that there was no significant difference between endocrine therapies. Further research is required to determine the short-and long-term effects of endocrine therapy on quality of life.

STRENGTHS AND WEAKNESS OF EVIDENCE

Only four trials^{7,10,17,18} investigating the use of endocrine therapy in post-menopausal women specifically recruited patients with hormone receptor-positive disease. Hormone receptor status of participants was not explicitly stated in the Schmid (2001)¹⁴ publication. In all other trials, patients with unknown hormone receptor status were eligible to participate in the trials. Across all studies there was no consistent definition of 'advanced breast cancer'.

The overall survival data from the included studies should be interpreted with caution due to the uncontrolled nature of treatment post-progression. In two post-menopausal trials patients crossed over to the alternate therapy on disease progression. In other trials, treatment following disease progression and study drug discontinuation was at the discretion of the investigator. Post-progression therapies may therefore have impacted on overall survival. Information about long-term results on overall survival and adverse events is not yet available.

Clinical practice recommendations developed by NBOCC will be reviewed and revised as required as additional significant evidence becomes available.

UNANSWERED QUESTIONS

Important unanswered questions about the use of endocrine therapy in hormone receptor-positive advanced breast cancer are outlined below; some of these may be addressed in ongoing trials:

- the use of third generation aromatase inhibitors and fulvestrant in pre-menopausal women
- which endocrine therapy is recommended for women who have progressed on adjuvant aromatase inhibitors
- the relative benefits and harms of different aromatase inhibitors
- the relative benefits and harms of fulvestrant
- quality-of-life issues associated with endocrine therapy
- long-term side effects associated with the use of endocrine therapy.

ONGOING AND ADDITIONAL TRIALS

A number of ongoing randomised trials are investigating the use of endocrine therapy in hormone receptor-positive advanced breast cancer:

- four ongoing trials investigating the use of endocrine therapy in pre-menopausal women with advanced breast cancer (D8664C00008, Zoladex ABC Study,²⁴ FHCRC-6412, UWCC-UW 6412,²⁵ SWOG-8692,²⁶ MSHMC-1609)
- three ongoing trials investigating the use of endocrine therapy as first-line therapy for advanced breast cancer (FIRST,²⁷ SWOG-S0226,²⁸ EORTC-10951²⁹)
- three ongoing trials investigating the use of endocrine therapy as second-line therapy for advanced breast cancer (ICR-CTSU Sofea,³⁰ D6997L00004,³¹ EFECT³²)
- two ongoing trials comparing one aromatase inhibitor with another in advanced breast cancer (A5991048,³³ GEICAM 2001-03.³⁴)

REFERENCES

- 1 National Breast Cancer Centre. Clinical practice guidelines for the management of advanced breast cancer. Canberra: Commonwealth of Australia 2001.
- 2 Klijn JGM, Blamey RW, Boccardo F, et al. Combined tamoxifen and luteinizing hormone-releasing hormone (LH-RH) agonist versus LH-RH agonist alone in premenopausal advanced breast cancer: A meta-analysis of four randomized trials. *J Clin Oncol* 2001;19(2):343–353.
- 3 National Breast and Ovarian Cancer Centre. Evidence of the use of endocrine therapy for postmenopausal women with metastatic breast cancer. National Breast and Ovarian Cancer Centre, Surry Hills, NSW, 2008.
- 4 Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy alone versus endocrine therapy alone for metastatic breast cancer. *Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD002747. DOI: 10.1002/14651858.CD002747.
- 5 Klijn JGM, Beex VAM, Mauriac L, et al. Combined Treatment With Buserelin and Tamoxifen in Premenopausal Metastatic Breast Cancer: A Randomised Study. *J Nat Cancer Inst* 2000; 92 (11): 903–911.
- 6 Bonneterre J, Buzdar A, Nabholz JA, et al. Anastrozole is superior to tamoxifen as first-line therapy in hormone receptor positive advanced breast carcinoma. *Cancer* 2001;92(9):2247–58.
- 7 Milla-Santos A, Milla L, Portella J, et al. Anastrozole versus tamoxifen as first-line therapy in postmenopausal patients with hormone-dependent advanced breast cancer. *A J Clin Oncol* 2003; 26(3):317–22.
- 8 Paridaens R, Dirix L, Lohrisch C, et al. Mature results of a randomized phase II multicenter study of exemestane versus tamoxifen as first-line hormone therapy for postmenopausal women with metastatic breast cancer. *Ann Oncol* 2003;14:1391–8.
- 9 Mouridsen H, Gershanovich M, Sun Y, et al. Superior efficacy of letrozole versus tamoxifen as first-line therapy for postmenopausal women with advanced breast cancer: results of a phase III study of the international letrozole breast cancer group. *J Clin Oncol* 2001;19(10):2596–606.
- 10 Batra U, Jacob LA, Saini KS, Dadhich HK. To analyze the efficacy, tolerability and pharmacoeconomics of letrozole vs. tamoxifen as first-line therapy in post menopausal, hormone positive females with metastatic or recurrent breast cancer. *Ann Oncol* 2006;17(Suppl 9): ix77.
- 11 Buzdar A, Jonat W, Howell A, et al. Anastrozole, a potent and selective aromatase inhibitor, versus megestrol acetate in postmenopausal women with advanced breast cancer: results of overview analysis of two phase III trials. *J Clin Oncol* 1996;14(2000–11).
- 12 Kaufmann M, Bajetta E, Dirix LY, et al. Exemestane improves survival compared with megestrol acetate in postmenopausal patients with advanced breast cancer who have failed on tamoxifen: results of a double-blind randomised phase III trial. *Euro Cancer* 2000;36(Suppl):81–91.
- 13 Buzdar A, Douma J, Davidson N, et al. Phase III, multicenter, double-blind, randomized study of letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001;19(14):3357–66.
- 14 Schmid P, Wischnewsky MB, Possinger K. Self organizing maps and prognosis of advanced breast cancer patients with bone metastases receiving letrozole or MA. *Breast Cancer Res and Treat* 2001;64:77.

- 15 Dombernowsky P, Smith I, Falkson G, et al. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double-blind randomized trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998;16(2):453–61.
- 16 Mauriac L, Pippen JE, Quaresma Albano J, Gertler SZ, Osborne CK. Fulvestrant (Faslodex) versus anastrozole for the second-line treatment of advanced breast cancer in subgroups of postmenopausal women with visceral and non-visceral metastases: combined results from two multicentre trials. *Euro J Cancer* 2003;39(9):1228–33.
- 17 Gradishar W, Chia S, Piccart M, on behalf of the EFECT writing committee. Fulvestrant versus exemestane following prior non-steroidal aromatase inhibitor therapy: first results from EFECT, a randomized, phase III trial in postmenopausal women with advanced breast cancer. 29th Annual San Antonio Breast Cancer Symposium, December 2006, Abstract 12.
- 18 Mayordomo J, Llombart A, Martin M, et al. Randomized, multicenter, crossover phase II trial to compare exemestane (E) vs. anastrozole (A) in postmenopausal patients (pt) with advanced breast cancer (ABC) and positive hormone receptors (HR). Final efficacy analysis of GEICAM 2001-03 study. ASCO Annual Meeting 2006, abstract no. 638.
- 19 Rose C, Vtoraya O, Pluzanska A, et al. An open randomised trial of second-line endocrine therapy in advanced breast cancer. *Euro J Cancer* 2003;39(16):2318–27.
- 20 National Health and Medical Research Council. How to use the evidence: assessment and application of scientific evidence. Canberra, Commonwealth of Australia, 2000.
- 21 National Breast Cancer Centre. Recommendations for use of Trastuzumab (Herceptin®) for treatment of HER2-positive breast cancer. NBCC, Camperdown, NSW, 2007.
- 22 National Breast Cancer Centre and National Cancer Control Initiative. Clinical practice guidelines for the psychosocial care of adults with cancer. NBCC, Camperdown, NSW, 2003.
- 23 Therapeutic Good Administration <http://www.tga.gov.au/> Accessed October 10, 2007.
- 24 National Cancer Institute Clinical Trials (PDQ®) D8664C00008, Zoladex ABC Study <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=484695&version=patient&protocolsearchid=3592790> Accessed August 31, 2007.
- 25 National Cancer Institute Clinical Trials (PDQ®) UWCC-UW 6412 <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=553612&version=patient&protocolsearchid=3592790> Accessed August 31, 2007.
- 26 National Cancer Institute Clinical Trials (PDQ®) SWOG-8692 http://www.nci.nih.gov/clinicaltrials/view_clinicaltrials.aspx?version=healthprofessional&cdrid=74317&protocolsearchid=842037 Accessed August 31, 2007.
- 27 National Cancer Institute Clinical Trials (PDQ®) FIRST <http://clinicaltrials.gov/ct/show/NCT00274469?order=1> Accessed August 31, 2007.
- 28 National Cancer Institute Clinical Trials (PDQ®) SWOG-S0226 <http://www.cancer.gov/clinicaltrials/SWOG-S0226> Accessed August 31, 2007.
- 29 National Cancer Institute Clinical Trials (PDQ®) EORTC-10951 <http://www.cancer.gov/clinicaltrials/EORTC-10951> Accessed August 31, 2007.
- 30 National Cancer Institute Clinical Trials (PDQ®) ICR-CTSU Sofea <http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=448616&version=patient&protocolsearchid=3592790> Accessed August 31, 2007.

- 31 National Cancer Institute Clinical Trials (PDQ®) D6997L00004
<http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=487687&version=HealthProfessional&protocolsearchid=3594517> Accessed August 31, 2007.
- 32 Clinical Trials EFACT
<http://clinicaltrials.gov/ct/show/NCT00065325?order=1> Accessed August 31, 2007.
- 33 National Cancer Institute Clinical Trials (PDQ®) A5991048
<http://www.cancer.gov/search/ViewClinicalTrials.aspx?cdrid=447079&version=patient&protocolsearchid=3592790> Accessed August 31, 2007.
- 34 GEICAM 2001-03 <http://www.geicam.org/ingles/protocolgeicam2001-03.htm>
Accessed August 31, 2007.

Membership of NBOCC Endocrine Therapy Subgroup

This guideline was developed by a multidisciplinary working group convened by NBOCC:

Dr Catherine Shannon	Medical Oncologist (Chair)
Ms Denice Bassanelli	Consumer Representative
Dr Richard De Boer	Medical Oncologist
Dr Nicole McCarthy	Medical Oncologist
Ms Janet Rice	Nurse
Professor Patsy Yates	Nurse

Membership of NBOCC Advanced Breast Cancer Guidelines Working Group

The development of this guideline was overseen by a multidisciplinary working group convened by NBOCC: Dr Karen Luxford (Facilitator), Dr David Blakey, Professor Phyllis Butow, Ms Helen Collyner, Ms Sally Crossing, Associate Professor Jane Dahlstrom, Dr Craig Murphy, Ms Janet Rice, Dr Catherine Shannon, Ms Ann Town, Professor Patsy Yates

NBOCC Staff

Ms Ornella Care	Senior Project Officer (Project lead)
Dr Karen Luxford	General Manager
Ms Alison Pearce	Program Manager

Systematic review

NBOCC gratefully acknowledges the work of Dr Suzanne Campbell at Health Technology Analyst Pty Ltd in developing the systematic review *Evidence on the use of endocrine therapy for post-menopausal women with metastatic breast cancer (2008)*, which informed the development of this guideline

External Review

NBOCC acknowledges those who gave their time to provide comment on the draft guideline recommendations as part of the external review process

Acknowledgement

The National Breast Cancer Foundation provided funding for the development and production of this guideline



Pharmaceutical Benefits Scheme indications for drugs mentioned in this guideline (as of 1 March 2008). For updates after this date go to <http://www.pbs.gov.au>

Anastrozole:	Treatment of hormone-dependent breast cancer in post-menopausal women
Exemestane:	Treatment of hormone-dependent advanced breast cancer in post-menopausal women with disease progression following treatment with tamoxifen citrate
Letrozole:	Treatment of hormone-dependent advanced breast cancer in post-menopausal women
Goserelin:	Hormone-dependent locally advanced (equivalent to stage III) or metastatic (equivalent to stage IV) breast cancer in pre-menopausal women
Megestrol acetate:	Treatment of hormone-dependent advanced breast cancer
Tamoxifen:	Treatment of hormone-dependent breast cancer. This drug is not subsidised for the primary prevention of breast cancer

Full details of trial results are provided in the document *Evidence on the use of endocrine therapy for post-menopausal women with metastatic breast cancer (2008)*, which can be accessed via the NBOCC website at www.nbocc.org.au

ISBN Print: 978-1-74127-089-1 Online: 978-1-74127-094-5 CIP: 11545

© National Breast and Ovarian Cancer Centre 2008

Locked Bag 3 Strawberry Hills NSW 2012 Australia
Suite 103, 355 Crown Street Surry Hills NSW 2010
Telephone: +61 2 9357 9400 Fax: +61 2 9357 9477
Website: www.nbocc.org.au Email: directorate@nbocc.org.au

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from National Breast and Ovarian Cancer Centre. Requests and enquiries concerning reproduction and rights should be addressed to the Public Affairs Manager, National Breast and Ovarian Cancer Centre, Locked Bag 3 Strawberry Hills NSW 2012 Australia.

National Breast and Ovarian Cancer Centre is funded by the Australian Government Department of Health and Ageing.

www.nbocc.org.au

© National Breast and Ovarian Cancer Centre 2008

Funded by the Australian Government Department of Health and Ageing