

Breast cancer diagnosis and treatment: an update

Epidemiology

Breast cancer is the most common cancer in the UK.¹ There are approximately 44,600 women and 300 men diagnosed each year in the UK.¹ More than 12,000 women and approximately 100 men die from breast cancer in the UK each year, making it the second most common cause of death in women after lung cancer.¹

Types of breast cancer

An early form of breast cancer in which there is evidence of cancerous cells within the ducts (ductal cancer *in situ*) is highly localised with no spread to the surrounding breast tissue.¹ If left untreated, however, this can develop into invasive ductal breast cancer — the cause of around 70–80% of cases. Similarly, carcinomatous cells can develop in cells lining the lobules, without spread, but around 10% of breast cancers are invasive lobular cancers, and these are

more common in women aged 45–55 years but rare in men.

Familial breast cancer, accounting for 5–10% of all cases, is caused by the inheritance of one of the mutated genes; *BRCA1*, *BRCA2*, *TP53* or *PTEN*.¹ Around two-thirds of women have hormone-receptor positive tumours, in which endogenous oestrogen and progesterone promote tumour growth.¹ Some cancers test positive for human epidermal growth factor receptor-2 (HER2), which also promotes cancerous growth.¹ Inflammatory breast cancer in which cancer cells accumulate in lymph channels and ducts to cause blockage and acute inflammation, is rare.¹ Paget's disease is associated with 1–2% of cases.¹ It starts with an eczema-like rash, usually affecting the skin around one nipple. In 90% of such cases an underlying mass is present, which can be invasive.¹

Presentation

Breast cancer is most commonly diagnosed by breast screening in asymptomatic women or by self-examination. Warning signs may include any of the following:¹

- change in size, shape or feel of breasts
- the presence of a new lumpy mass that cannot be moved independently from overlying skin
- thickening in one breast or armpit
- any puckering, dimpling or redness of the skin
- changes in the position of nipple, nipple inversion, nipple rash or discharge
- a new one-sided pain or discomfort.

The NHS Breast Screening programme is perhaps one of the most successful in Europe, saving an estimated 1400 lives each year.² The programme has contributed

Table 1. Staging breast cancer³

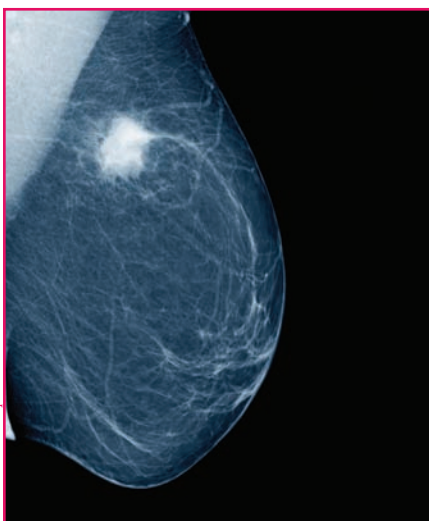
Stage	Description
I	Tumour measures <2cm. Lymph nodes in armpit unaffected. No signs that cancer has spread elsewhere in the body.
II	Tumour measures 2–5cm or lymph glands in armpit affected or both. No signs that cancer has spread further.
III	Tumour measures >5cm and may be attached to surrounding structures such as muscle or skin. Lymph glands are usually affected, but there are no signs that the cancer has spread beyond the breast or lymph glands in the armpit. This is locally advanced breast cancer that is further divided into stage IIIA, IIIB, IIIC depending on the degree of involvement with the lymph nodes or surrounding structures. Treatment may differ between each stage.
IV	Tumour is of any size, but lymph glands are usually affected and the cancer has spread to other parts of the body. This is secondary or metastatic breast cancer.

greatly to improved early detection and better treatment.²

Diagnosis

Investigations are usually undertaken in women who have noticed concerning changes in their breasts that cause them to consult their GP who, after examining the breasts will refer the patient to hospital or breast clinic for a full investigation. This will include a medical history and breast examination to feel for any enlarged lymph nodes at the base of the neck and armpits. Diagnostic tests include a mammogram, which is useful for finding early changes in the breasts where it may be difficult to feel a lump in women aged 50 years or more.

For younger women (particularly <35 years¹) an ultrasound is usually preferred, because their breasts are too dense to



give a clear view through mammography.¹ Ultrasound however, can determine whether the breast lump is solid or a cyst.¹

Subsequently, a biopsy may be taken — this may be to sample a few cells through fine needle aspiration cytology or to obtain core tissue from the lump using a larger needle biopsy and will allow a determination of malignancy of the tissue. Further scans may be carried out such as CT, MRI or PET scans if more detail is required and to check for secondaries.¹ An excision biopsy removes the whole lump for examination. Many women diagnosed with breast cancer will have surgery and various standard blood tests are carried out as part of a pre-operative screen, including:

- full blood count
- liver function tests
- calcium and alkaline phosphatase
- urea and electrolytes.

All patients should also be tested for the presence of oestrogen, progesterone and HER2-positive cells to see whether targeted therapy might be helpful. Once a diagnosis is made, the patient's cancer is staged and graded according to its progression to help decide which treatment regimen is most appropriate.

Stages and grading of breast cancer

The stage of breast cancer describes its size and whether it has spread beyond its original site. In terms of treating a patient the grade is considered less important than

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the stage but produces an idea of how quickly the cancer may develop and refers to the histological type of cancer cell.

Staging

Stage 0 is ductal carcinoma *in situ* (DCIS) where the cancer cells are completely contained within the breast ducts and this is almost always curable with treatment. Invasive breast cancer stages progress from stage I to stage IV as indicated in Table 1.³

Grading

There are three main grades of breast cancer as shown in Table 2.³

Treatment

The treatment depends on the stage and grade of cancer (whether this is an early stage local tumour, locally advanced or metastatic), a patient's age, menopausal status, whether the cancer is oestrogen-receptor positive (ER+) or HER2+, previous treatment experience, and their fitness and wishes.^{1,4} Systemic treatments should be guided by evidence-based guidelines that are reviewed regularly to incorporate current research. Where appropriate, patients should be invited to participate in well-designed clinical trials.⁴ In addition to radiotherapy; therapeutic options are either surgical, pharmaceutical or both.

Surgery

Surgical treatment is the main curative modality for primary breast cancer, where

Table 2. Grading breast cancer³

Grade	Description
1	Low grade. Cancer cells look similar to the normal cells of the breast. They are usually slow to grow and less likely to spread.
2	Moderate/intermediate grade
3	High grade. Tumour cells look abnormal. They are more likely to grow and spread quickly.

Table 3. Main agents used in breast cancer and their specific indications

Drug (Class)	Mechanism of action
Cyclophosphamide (Alkylating drug)	Interferes with cell replication by damaging DNA through alkylation.
5-Fluorouracil (Antimetabolite)	Pyrimidine antagonist. Uracil analogue that interferes with RNA synthesis. Interferes with DNA synthesis by inhibiting thymidylate synthesis.
Capecitabine (Antimetabolite)	Prodrug of 5-fluorouracil.
Gemcitabine (Antimetabolite)	Pyrimidine antagonist. DNA strand terminator. Inhibits RNA synthesis by disrupting the phosphorylation of nucleosides.
Methotrexate (Antimetabolite)	Folic acid antagonist. Inhibits dihydrofolate reductase (essential for thymidylate synthesis).
Epirubicin (Anthracycline)	Intercalates with planar ring of DNA to inhibit nucleic acid synthesis and mitosis.
Doxorubicin (Anthracycline)	DNA topoisomerase II inhibitor.
Mitomycin (Anthracycline)	Alkylates and cross-links with DNA disrupting its synthesis.
Mitoxantrone (Anthracenedione)	DNA topoisomerase II inhibitor.
Docetaxel (Taxane — diperpine)	Decreases presence of free tubulin by disrupting microtubule formation. Mitotic spindle formation is inhibited leading to mitotic arrest.
Paclitaxel (Taxane)	Disrupts organisation of microtubule network essential for mitosis.
Trastuzumab (Humanised monoclonal antibody)	Antibody against the protein HER2.
Vinorelbine (Vinka alkaloid)	Inhibits tubulin polymerisation and binds to mitotic microtubules causing mitotic arrest.

reconstruction should be available at surgery.⁴ Surgical interventions are generally either: lumpectomy, where small, localised tumours are removed along with minimal surrounding breast tissue; segmental excision, which is similar to lumpectomy but more of the surrounding tissue is removed, and mastectomy in which the whole breast is removed.¹

Radiotherapy

Radiotherapy lowers the risk of cancer recurring, either in the remaining breast tissue or in lymph nodes that are treated.⁵ Radiotherapy should be regarded as standard therapy for all women who have undergone breast conserving surgery, and considered for women who have had a mastectomy.⁴ Radiotherapy may also be given as neoadjuvant and adjuvant treatment, or as a sole treatment modality if surgery is inappropriate.⁴

Pharmaceutical therapies

Pharmaceutical agents, which will form the main focus of this review, include chemo-, hormonal and targeted therapies.

Chemotherapy

Chemotherapy involves using a variety of cytotoxic agents to halt tumour growth and/or destroy growing cancer cells. Chemotherapy can be given as neoadjuvant before surgery to shrink a tumour to make surgery easier/more successful, or as adjuvant after surgery to reduce the risk of disease relapse/recurrence, or for advanced disease as a palliative therapy to treat tumour spread.¹ The main classes of chemotherapies used

Table 4. Common combinations used to treat breast cancer

Combination	Evidence
CMF: Cyclophosphamide, Methotrexate, 5-FU	This traditional regimen is being replaced with anthracycline regimens which when compared to CMF, have shown increased absolute survival rates from 69% to 72% and reduced recurrence (12%). ⁴ This combination can be used if anthracycline therapy is inappropriate (e.g. cardiac disease). ²⁴
TAC: Docetaxel, Doxorubicin, Cyclophosphamide	Recommended as an option for adjuvant treatment with early node positive breast cancer. ^{24,25} However, sequential regimens of anthracyclines followed by docetaxel would be preferred because of their high toxicity.
Epirubicin followed by CMF FEC: Epirubicin, Cyclophosphamide, 5-FU MMM: Methotrexate, Mitoxantrone, Mitomycin MM: Methotrexate, Mitoxantrone AC: Doxorubicin, Cyclophosphamide	Adjuvant chemotherapy should include an anthracycline unless contra-indicated. Epirubicin with CMF is more effective than CMF alone. ⁴ Anthracycline and cyclophosphamide therapy is the standard initial therapy for metastatic breast cancer in women who have not previously received chemotherapy. ^{10,24}
Docetaxel/Paclitaxel (Taxanes)	Taxanes appear to be more effective than longer-established regimens using cyclophosphamide, 5-FU and doxorubicin or single-agent doxorubicin for metastatic breast cancer. They produce a better response rate and longer remission with an estimated increase in survival time of 20-25%. ⁴
Single trastuzumab/ Trastuzumab + Paclitaxel	Licensed for tumours highly expressive of HER2.

for breast cancer are alkylating agents, anthracyclines, antimetabolites and taxanes. The main chemotherapeutic agents are listed in Table 3 alongside their indications specific to breast cancer and associated NICE guidance.

Common combination therapies

A combination of chemotherapy agents has been shown to reduce annual recurrence rates and overall death rates by 28% and 17% respectively.³ Poly-chemotherapy is therefore favoured over monotherapy, especially in women aged less than 50 years and some of the common combinations used along with evidence to support this is summarised briefly in Table 4. There is insufficient evidence in women aged more than 70 years.³⁴

Dosing cycles

NICE recommends that adjuvant chemotherapy for breast cancer should consist of 4–8 cycles with multiple agents, including an anthracycline (epirubicin/doxorubicin). The optimum regimen remains unclear and variations in prescribing habits exist between oncologists.⁴

Hormonal therapies

Steroid hormone-receptor positive breast cancer can be managed with hormonal therapy and the main options are tamoxifen, aromatase inhibitors (AI's) and pituitary down-regulators. Hormone antagonists are used in pre-operative or post-operative breast cancer management, or recurrences.

Tamoxifen

Tamoxifen, the oestrogen receptor antagonist, is the treatment of choice in premenopausal, perimenopausal and postmenopausal women with metastatic breast

cancer.²⁴ Used alone or after surgery, it delays the development of metastases and has been the standard adjuvant hormonal treatment for postmenopausal women with early ER+ breast cancer when given for five years.³⁵ Adjuvant tamoxifen substantially improves the 10-year survival of women with ER+ breast cancer.³⁶

Aromatase inhibitors for postmenopausal women

AI's, taken daily, inhibit the conversion of androgen to oestrogen in peripheral tissues. They do not inhibit ovarian oestrogen synthesis and therefore, are effective only in postmenopausal women. Their use in early ER+ breast cancer in postmenopausal women has been reviewed previously in *Pharmacy in Practice* and readers are referred to this article for further information.³⁷ The AI's anastrozole, exemestane, and letrozole are all licensed as adjuvant therapy for early ER+ breast cancer for postmenopausal women.³⁵ NICE recommends the following options for early ER+ breast cancer:³⁵

- Anastrozole.** Primary adjuvant therapy. Also considered for women who have already received 2–3 years of adjuvant tamoxifen.³⁸
- Exemestane.** Recommended after 2–3 years of initial adjuvant treatment with tamoxifen.
- Letrozole.** First-line hormonal treatment and for extended hormone treatment after taking tamoxifen.

AI's also have a role in advanced breast cancer where anti-oestrogen therapy with tamoxifen has failed, as detailed in Table 5.

Table 5. Aromatase inhibitors and their indications

AI	Indication
Anastrozole	Advanced breast cancer in postmenopausal women. ^{38–41}
Exemestane	Advanced breast cancer in postmenopausal women whose disease progressed despite anti-oestrogen therapy. ^{42–45}
Letrozole	First-line treatment in postmenopausal women with advanced breast cancer. ^{46,47} Advanced breast cancer in postmenopausal women where tamoxifen or other anti-oestrogen therapy has failed. ^{48–51} Pre-operative therapy in postmenopausal women with localised hormone receptor positive breast cancer to allow breast-conserving surgery. ^{52,53}

Anastrozole and letrozole are at least as effective as tamoxifen for first-line treatment of metastatic breast cancer in postmenopausal women. However, it is not known whether their benefits persist in the long term.²⁴

NICE recommends adjuvant chemotherapy for breast cancer should consist of 4–8 cycles with multiple agents, including an anthracycline.

Pituitary down-regulators

Goserelin (Zoladex) is the most commonly used pituitary down-regulator. It is a luteinising hormone releasing hormone (LHRH) agonist. With chronic use it inhibits pituitary LH secretion leading to a fall in oestrogen and testosterone. Goserelin is licensed for the management of advanced breast cancer in and pre- and perimenopausal women.⁵⁴

Targeted therapies

This includes the monoclonal antibodies, trastuzumab (Herceptin) and the small molecule tyrosine kinase inhibitor lapatinib (Tykerb). Trastuzumab, which is licensed for early and advanced breast cancer, binds with the protein HER2/neu (also known as epidermal growth factor receptor-2 or erbB2 (Table 3)⁸ and thereby blocks its promotion

of tumour growth. Lapatinib binds to both HER2/neu receptors and to epidermal growth factor receptor-1 (erbB1) in breast tissue. Lapatinib is now licensed in the UK for metastatic disease in combination with capecitabine and is currently undergoing early clinical trials in adjuvant disease.

Trastuzumab was initially recommended for use in only advanced breast cancer by NICE.⁸ Because up to 25% of cases may test positive for HER2, the absence of a licence in early breast cancer was continuously questioned in light of promising clinical trials.^{55,56} This absence caused further controversy by the creation of a 'postcode lottery' where certain health authorities and hospitals would fund the treatment, which for each patient averages £21,500 PA.^{8,30} Consequently, final guidance from NICE was published soon after the licence in early breast cancer was accepted by the regulatory authorities in 2006.³⁰

Future research

Numerous clinical trials are underway to evaluate existing and novel therapeutic

agents or management strategies for breast cancer. To illustrate the breadth of these studies a selection of some of the current clinical trials is given in Table 6.

Summary

Chemotherapy treatment options for breast cancer offer a good degree of choice of single agents or combinations, tailored to the type of cancer and its degree of progression. Adjuvant chemotherapy should be offered in 4–8 cycles of multiple-agent chemotherapy, which should include anthracyclines. If anthracycline therapy has failed or is contraindicated, capecitabine is an option for locally advanced or metastatic breast cancer. Vinorelbine monotherapy or gemcitabine and paclitaxel are other options in metastatic breast cancer.

Taxanes are recommended as an option for advanced breast cancer where initial chemotherapy with anthracyclines has failed. They are not licensed for adjuvant treatment in early breast cancer, but are combined with trastuzumab in metastatic breast cancer where anthracycline therapy has failed. Trastuzumab is also used as monotherapy in early and metastatic breast cancer.

All women with hormone receptor-positive tumours should be offered hormone treatment for five years after primary therapy. This is likely to involve tamoxifen, or an AI plus ovarian ablation or an LHRH agonist for pre-menopausal women.

Clinical guidelines on the diagnosis and treatment of early and advanced breast cancer are currently pending from NICE. The clinical trials mentioned in this overview of breast cancer management represent a selection of the main trials in progress, which will no doubt contribute to the evidence base for the development of future breast cancer management strategies. ❖

Declaration of competing interests

The author declares she has no competing interests.

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Table 6. Some ongoing clinical trials

Carboplatin and Gemcitabine chemotherapy for breast cancer resistant to anthracyclines and taxane chemotherapy. Phase II trial. Aims to assess the effectiveness of this combination as gemcitabine is already used in combination but carboplatin is not.⁵⁷

TACT2 trial: Comparing two weekly and three weekly epirubicin combined with either CMF or capecitabine after surgery for breast cancer. Phase III trial. Aims to assess the efficacy of accelerated treatment with the addition of capecitabine.⁵⁷

SOFEA trial: Hormone therapy for advanced breast cancer. Phase III trial. Involves fulvestrant which down-regulates oestrogen receptors and is an oestrogen antagonist. Aims to assess superiority of fulvestrant vs. anastrozole, fulvestrant vs. placebo and exemestane in advanced breast cancer unresponsive to AI therapy.⁵⁷

TNT trial: Triple Negative breast cancer. Phase III trial. Carboplatin is compared to docetaxel for metastatic or recurrent locally advanced ER-, PR- and HER2- breast cancer.⁵⁷

ACTION trial: Adjuvant chemotherapy in older women. Phase III trial. Aims to assess adjuvant chemotherapy in women aged more than 70 years, and whether accelerated therapy with GCSF support will not cause undue toxicity in this group.⁵⁷

SOFT trial: Suppression of ovarian function. Phase III trial. Aims to assess efficacy of tamoxifen alone, tamoxifen and ovarian ablation, and exemestane and ovarian ablation.⁵⁷

PERSEPHONE trial: Duration of trastuzumab. Phase III trial. Aims to assess whether women with early breast cancer can safely have trastuzumab for 6 months instead of 12 months to help lower the risk of cardiac damage.⁵⁷

ASBO study: Phase II trial. Single-arm trial of pertuzumab (HER2 dimerisation inhibitor) and trastuzumab in HER2+ metastatic breast cancer. Promising results recently show patients whose disease progressed with trastuzumab benefited with combined monoclonal antibody therapy. This combination is also being evaluated against chemotherapy in the CLEOPATRA trial.⁵⁸

TBP study: Phase III trial. Aims to assess trastuzumab treatment in patients with HER2+ metastatic breast cancer requiring subsequent lines of treatment. Recent results showed a significant improvement by continuing on trastuzumab in combination with oral capecitabine compared with capecitabine alone.⁵⁹

References

- Cancer Research UK. Information on breast cancer incidence, diagnosis and treatments is available from www.cancerresearchuk.org/cancerstats/?a=5441 and its sister website <http://www.cancerhelp.org.uk/help/default.asp?page=3266> accessed 15/5/2008.
- Information on cancer screening is available from www.cancerscreening.nhs.uk/breastscreen/index.html accessed 19/6/08.
- Information on cancer diagnosis and staging is available from www.cancerbackup.org.uk/cancertype/breast/causediagnosis/staginggrading accessed 18/5/2008.
- National Institute for Health and Clinical Excellence. *Improving outcomes in breast cancer. Cancer Service Guideline*. Aug 2002. Accessed from www.nice.org.uk on 27/5/8.
- Cochrane Database for Systematic Reviews. Early Breast Cancer Trialists' Collaborative Group. *Radiotherapy for early breast cancer*, 2002, Issue 2. Accessed from www.cochrane.org/reviews on 21/6/8.
- Poole-Christopher J *et al*. Epirubicin and cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy for early breast cancer. *New Eng J Med* 2006; **355**(18): 1851-62.
- Langley-Ruth E *et al*. Phase III trial of epirubicin plus paclitaxel compared with epirubicin plus cyclophosphamide as first line chemotherapy for metastatic breast cancer: United Kingdom National Cancer Research Institute Trial AB01. *J Clin Oncol* 2005; **23**(33): 8322-30.
- National Institute for Health and Clinical Excellence. *Guidance on the use of trastuzumab for the treatment of advanced breast cancer*. TA34. Mar 2002. Accessed from www.nice.org.uk on 1/6/08.
- Bonadonna G *et al*. Adjuvant cyclophosphamide, methotrexate and fluorouracil in node-positive breast cancer. The results of 20 years of follow-up. *New Eng J Med* 1995; **332**(14): 901-6.
- Zielinski C *et al*. Gemcitabine, epirubicin and paclitaxel versus fluorouracil, epirubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: A central European co-operative oncology group international multicentre prospective randomised phase III trial. *J Clin Oncol* 2005; **23**(7): 1401-8.
- National Institute for Health and Clinical Excellence. *Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer*. TA62. May 2003. [Accessed from www.nice.org.uk on 27/5/2008.]
- O'Shaughnessy J *et al*. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: Phase III trial results. *J Clin Oncol* 2002; **20**(12): 2812-23.
- Blum JL *et al*. Multicenter Phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. *J Clin Oncol* 1999; **17**: 485-93.
- Blum JL *et al*. Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast cancer carcinoma patients. *Cancer* 2001; **92**: 1759-68.
- Reichardt P *et al*. Multicenter phase II study of oral capecitabine (Xeloda) in patients with metastatic breast cancer relapsing after treatment with a taxane-containing therapy. *Ann Oncol* 2003; **14**: 1227-33.
- Summary of Product Characteristics. *Capecitabine (Xeloda)*. Accessed from www.medicines.org.uk on 1/6/8.
- Summary of Product Characteristics. *Gemcitabine (Gemzar)*. Accessed from www.medicines.org.uk on 1/6/8.
- National Institute for Health and Clinical Excellence. *Gemcitabine for the treatment of metastatic breast cancer*. TA116. Jan 2007. Accessed from www.nice.org.uk on 1/6/8.
- Summary of product characteristics. *Methotrexate 10mg/ml injection*. Accessed from www.medicines.org.uk on 1/6/08.
- Summary of product characteristics. *Epirubicin 2mg/ml injection*. Accessed from www.medicines.org.uk on 1/6/08.
- Summary of product characteristics. *Caelyx (doxorubicin) 2mg/ml injection*. Accessed from www.medicines.org.uk on 1/6/08.
- Summary of product characteristics. *Mitomycin-C Kyowa*. Accessed from www.medicines.org.uk on 10/6/8.
- Legha SS *et al*. A review of mitomycin regimens in advanced breast cancer therapy. *Clin Therapeut* 1985; **7**(3): 286-307.
- British Medical Association and Royal Pharmaceutical Society of Great Britain. *British National Formulary* 55, March 2008.
- National Institute for Health and Clinical Excellence. *Docetaxel for the adjuvant treatment of early node-positive breast cancer*. TA109. Sep 2006.
- National Institute for Health and Clinical Excellence. *Guidance on the use of taxanes for the treatment of breast cancer*. TA30. Sep 2001. Accessed from www.nice.org.uk on 1/6/08.
- Summary of product characteristics. *Taxotere (docetaxel)*. Accessed from www.medicines.org.uk on 1/6/08.
- Summary of product characteristics. *Paclitaxel*. Accessed from www.medicines.org.uk on 1/6/08.
- National Institute for Health and Clinical Excellence. *Paclitaxel for the adjuvant treatment of early node-positive breast cancer*. TA108. Sep 2006. Accessed from www.nice.org.uk on 1/6/08.
- National Institute for Health and Clinical Excellence. *Trastuzumab for the adjuvant treatment of early-stage HER2 positive breast cancer*. TA107. Aug 2006. Accessed from www.nice.org.uk on 1/6/08.
- National Institute for Health and Clinical Excellence. *Guidance on the use of vinorelbine for the treatment of advanced breast cancer*. TA54. Dec 2002. Accessed from www.nice.org.uk on 1/6/08.
- Joensuu MD *et al*. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *New Eng J Med* 2006; **354**(8): 809-820.
- Chan A *et al*. Vinorelbine plus trastuzumab combination as first-line therapy for HER2-positive metastatic breast cancer: an international phase II trial. *Brit J Cancer* 2006, **95**: 788-793.
- Cochrane Database for Systematic Reviews. Early Breast Cancer Trialists' Collaborative Group. *Multi-agent chemotherapy for early breast cancer*. 2001, Issue 4. Accessed from www.cochrane.org/reviews/ on 24/5/8.
- National Institute for Health and Clinical Excellence. *Hormonal therapies for the adjuvant treatment of early oestrogen-receptor-positive breast cancer*. TA112. Nov 2006. Accessed from www.nice.org.uk on 1/6/08.
- Cochrane Database for Systematic Reviews. Early Breast Cancer Trialists Collaborative Group. *Tamoxifen for early breast cancer*. 2001, Issue 1. Accessed from www.cochrane.org/reviews/ on 1/6/8.
- Saunders G. Early oestrogen receptor-positive breast cancer in postmenopausal women may be treated with aromatase inhibitors. *Pharm in Pract* 2007; **17**(6): 173-7.
- Summary of product characteristics. *Anastrozole*. Accessed from www.medicines.org.uk on 1/6/08.
- Bonnetterre J *et al*. Anastrozole versus tamoxifen as first-line therapy for advanced breast cancer in 668 postmenopausal women: results of the tamoxifen or Arimidex randomised group efficacy and tolerability study. *J Clin Oncol* 2000; **18**(22): 3748-57.
- Nabholtz JM *et al*. Anastrozole is superior to tamoxifen as first-line therapy for advanced breast cancer in postmenopausal women: results of a North American multicentre randomised trial. *J Clin Oncol* 2000; **18**(22): 3758-67.
- Bonnetterre JM *et al*. Anastrozole is superior to tamoxifen as first-line therapy in hormone-receptor positive advanced breast carcinoma: results of two randomised trials designed for combined analysis. *Cancer* 2001; **92**(9): 2247-58.
- Summary of product characteristics. *Exemestane*. Accessed from www.medicines.org.uk on 1/6/08.
- Kvinnslund S *et al*. High activity and tolerability demonstrated for exemestane in postmenopausal women with metastatic breast cancer that have failed on tamoxifen treatment. *Eur J Cancer* 2000; **36**(8): 976-82.
- Lonning P *et al*. Activity of exemestane in metastatic breast cancer after failure of non-steroidal aromatase inhibitors. Phase II. *J Clin Oncol* 2000; **18**(11): 2234-44.
- Kausmann M *et al*. Exemestane is superior to megestrol acetate after tamoxifen failure in postmenopausal women with advanced breast cancer. Results of Phase III randomised double-blind trial. *J Clin Oncol* 2000, **18**: 1399-1411.
- Mouridsen H *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.
- Mouridsen H *et al*. Phase III study of letrozole versus tamoxifen as first-line therapy of advanced breast cancer in postmenopausal women: analysis of survival and update of efficacy from the International Letrozole Breast Cancer Group. *J Clin Oncol* 2003; **21**(11): 2101-9.
- Rose C *et al*. An open randomised trial of second-line endocrine therapy in advanced breast cancer. Comparison of the aromatase inhibitors letrozole and anastrozole. *Eur J Cancer* 2003; **39**(16): 2318-27.
- Dombernowsky P *et al*. Letrozole, a new oral aromatase inhibitor for advanced breast cancer: double blind, randomised trial showing a dose effect and improved efficacy and tolerability compared with megestrol acetate. *J Clin Oncol* 1998; **16**(2): 453-61.
- Buzdar A *et al*. Phase III multicentre, double-blind, randomised study of Letrozole, an aromatase inhibitor, for advanced breast cancer versus megestrol acetate. *J Clin Oncol* 2001; **19**(14): 3357-66.
- Gershanovich M *et al*. Letrozole, a new oral aromatase inhibitor: randomised trial comparing 2.5mg daily, 0.5mg daily and aminoglutethimide in postmenopausal women with advanced breast cancer. Letrozole International Trial Group (AR/BC3). *Ann Oncol* 1998; **9**(6): 639-45.
- Eiermann W *et al*. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomised double-blind multicentre study. *Ann Oncol* 2001; **12**(11): 1527-32.
- Summary of product characteristics. *Letrozole*. Accessed from www.medicines.org.uk on 1/6/8.
- Summary of product characteristics. *Goserelin 3.6mg*. Accessed from www.medicines.org.uk on 1/6/08.
- Romond EH *et al*. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *New Eng J Med* 2005; **353**(16): 1673-84.
- Piccari-Gebhart MJ *et al*. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *New Eng J Med* 2005; **353**(16): 1659-72.
- Information on current clinical trials is available from <http://www.cancerhelp.org.uk/trials/trials/selectsearch.asp> [Accessed 30/5/8]
- Gelman K *et al*. Results of a phase II trial of trastuzumab and pertuzumab in patients with HER2 positive metastatic breast cancer who had progressed during trastuzumab therapy. *J Clin Oncology* 2008; **26**: May 20 suppl: abstr 1026.
- Von Minckwitz G *et al*. Capecitabine versus capecitabine plus trastuzumab in patients with HER2 positive metastatic breast cancer progressing during trastuzumab treatment: The TBP Phase III study. *J Clin Oncology* 2008, **26**: May 20 suppl, abstr 1025.