NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

Review consultation document

Review of Clinical Guideline (CG81) – Advanced breast cancer: diagnosis and treatment

1. Background information

Guideline issue date: 2009
3 year review: 2012
National Collaborating Centre: Cancer

2. Consideration of the evidence

Literature search

Through an assessment of abstracts from a high-level randomised control trial (RCT) search, new evidence was identified related to the following clinical areas within the guideline:

- Systemic disease-modifying therapy
    - Endocrine therapy
    - Chemotherapy
    - Biological therapy
- Community based treatment and supportive care
- Managing complications

Through this stage of the process, a sufficient number of studies relevant to the above clinical areas were identified from the high level RCT search to

allow an assessment for a proposed review decision and are summarised in Table 1 below.

From initial intelligence gathering, qualitative feedback from other NICE departments, the views expressed by the Guideline Development Group, as well as the high-level RCT search, additional focused literature searches were also conducted for the following clinical areas:

- Diagnosis and assessment
- Managing complications: diagnosis and management of lymphoedema

The results of the focused search are summarised in Table 2 below. All references identified through the high-level RCT search, initial intelligence gathering and the focused searches can be viewed in Appendix 1.

Table 1: Summary of articles from the high level RCT search

Clinical area 1: Systemic disease-modifying therapy (endocrine therapy)		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the most effective hormone treatment for (1) women and (2) men with metastatic breast cancer? **Relevant section of the guideline and recommendations** Chapter 4: Systemic disease-modifying therapy - endocrine therapy	Through an assessment of abstracts from the high-level RCT search, 19 studies relevant to the clinical questions were identified. <u>Endocrine therapy – monotherapies (11 studies)</u> *Fulvestrant (Five studies)* • Five studies were identified relating to fulvestrant for treatment of advanced breast cancer.[1,2,3,4,5] Recommendations on the use of fulvestrant for breast cancer can be found in the recently published Technology Appraisal TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011. *Aromatase inhibitors (Three studies)*	This section of the guideline needs to cross refer to a new technology appraisal that was previously not mentioned in the guideline - TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011.

	• A systematic review assessed the use of steroidal (SAIs) and non-steroidal aromatase inhibitors (NSAIs) in metastatic breast cancer.[6] The review concluded that switching from an NSAI to a SAI could be a reasonable option. • A Cochrane systematic review assessed evidence comparing aromatase inhibitors with other endocrine therapy in the treatment of advanced breast cancer in postmenopausal women.[7] The review concluded that aromatase inhibitors show a survival benefit compared to other endocrine therapy for advanced breast cancer. • Lastly, a third systematic review evaluated the efficacy and safety of first-line aromatase inhibitors (letrozole, exemestane and anastrazole) in hormone sensitive advanced breast cancer concluding that additional head-to-head comparisons are warranted.[8] In summary, the identified new literature relating to aromatase inhibitors for treatment of advanced breast cancer indicates a	

	benefit of this therapy. As such, the identified new evidence is unlikely to change the direction of current guideline recommendations which state that steroidal or non-steroidal aromatase inhibitors should be offered to postmenopausal women with ER-positive breast cancer. *Exemestane (Two studies)* • Two RCTs compared exemestane with exemestane plus celecoxib in postmenopausal women with advanced breast cancer concluding that time to progression was similar in both groups.[9,10] *Estradiol (One study)* • One RCT was identified which aimed to determine whether estradiol (6 mg daily versus 30 mg) is a viable therapy for postmenopausal women with advanced aromatase inhibitor-resistant hormone receptor-positive breast cancer.[11] The study concluded that 6 mg of estradiol provided a similar	

	clinical benefit as 30 mg with fewer serious adverse effects. <u>Endocrine therapy versus endocrine therapy (Eight studies)</u> *Fulvestrant versus exemestane (Two studies)* • Two studies comparing fulvestrant with exemestane in patients with advanced breast cancer indicated similar clinical benefit of both therapies.[12,13] *Fulvestrant versus anastrazole (Two studies)* • The clinical activity of fulvestrant compared with anastrazole as a first-line endocrine therapy for postmenopausal women with advanced breast cancer was assessed in an RCT.[14] The clinical benefit rate and objective response rate were similar for the two therapies although time to progression was longer for fulvestrant. The results of a second RCT also indicated that fulvestrant and anastrazole were similarly effective.[15] *Exemestane versus tamoxifen (One study)*	

	• The efficacy and safety of exemestane compared with tamoxifen in postmenopausal women with metastatic breast cancer was assessed in an RCT.[16] Exemestane demonstrated significant early improvement compared with tamoxifen although no longer-term benefit in progression-free survival was observed. *Letrozole versus tamoxifen (One study)* • One RCT was identified which compared serum tissue inhibitor of metalloproteinases-1 (TIMP-1) levels in advanced breast cancer patients receiving letrozole or tamoxifen.[17] Letrozole was superior to tamoxifen in both the normal serum TIMP-1 group and the elevated serum TIMP-1 group. *Aromatase inhibitor versus tamoxifen (One study)* • A meta-analysis compared endpoints of aromatase inhibitors with tamoxifen in postmenopausal women with advanced breast cancer.[18] Aromatase inhibitors were favourable over	

	tamoxifen for overall response rate and clinical benefit whereas the trend towards improved overall survival was not significant. *Anastrazole versus exemestane (One study)* • One RCT was identified which evaluated the efficacy of anastrazole compared with exemestane in postmenopausal women with advanced breast cancer.[19] The results of the study indicated that efficacy was similar in both treatment groups for all endpoints assessed. **Summary** In summary, for some treatments only single trials were identified therefore further study is warranted to confirm the results obtained. Some new evidence was identified which compared the efficacy and safety of endocrine therapies for advanced breast cancer however, it would be pertinent to await additional evidence to confirm the results. In addition, a relevant Technology Appraisal relating to	

	fulvestrant as treatment for advanced breast cancer was identified. Therefore, there needs to be consideration of cross-referral to the relevant Technology Appraisal (TA239) that was previously not mentioned in the guideline.	
Clinical area 2: Systemic disease-modifying therapy (chemotherapy)		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the most effective chemotherapeutic treatment for (1) women and (2) men with metastatic breast cancer? **Relevant section of the guideline and recommendations** Chapter 4: Systemic disease-modifying therapy -	Through an assessment of abstracts from the high-level RCT search, 71 studies relevant to the clinical questions were identified. <u>Health economics studies (Six studies)</u> • A systematic review (focusing on the economic impact of metastatic breast cancer) and five cost-effectiveness analyses (evaluating the costs of different chemotherapy treatment regimens) were identified.[20,21,22,23,24,25] The studies evaluated the cost impact of different treatment regimens with several studies suggesting that docetaxel treatment was	No conclusive new evidence was identified which would invalidate current guideline recommendation(s).

chemotherapy	the least costly which is in line with the current guideline. In addition, two economic analyses of albumin-bound paclitaxel concluded that this could be an economically reasonable alternative to docetaxel for advanced breast cancer. Currently the guideline recommends using single-agent docetaxel as first line treatment for advanced breast cancer whereas the use of paclitaxel as a monotherapy is not included in the guideline recommendations. <u>Chemotherapy – general studies (14 studies)</u> *Chemotherapy regimens (Six studies)* • A systematic review was identified which compared chemotherapy regimens for metastatic breast cancer.[26] The review concluded that there is little evidence from published trials that major survival differences exist between commonly used chemotherapy regimens. Similarly, a systematic review concluded that currently available clinical evidence does not suggest one conventional chemotherapy regimen as	

	superior.[27] • A systematic review was identified which evaluated the clinical efficacy of cytotoxic agents in patients with locally advanced or metastatic breast cancer pretreated with an anthracycline and a taxane however, limited evidence was identified.[28] • A retrospective analysis was identified which carried out a long-term follow up of patients who had received chemotherapy for metastatic breast cancer.[29] Improvement in survival was observed in patients who had received an increased number of treatment regimens. • One RCT was identified which concluded that antiangiogenic treatment with sunitinib consolidation did not prolong remissions induced by taxane-based chemotherapy in women with metastatic breast cancer and led to significant toxicity.[30] • One meta-analysis compared primary and secondary end	

	points of taxane-based doublet with single-agent taxane chemotherapy in patients with advanced breast cancer and prior anthracycline treatment.[31] The results of the meta-analysis indicated that taxane-based doublet appeared to improve progression free survival compared with single-agent taxane in this population. In summary, several studies were identified which evaluated the efficacy of a variety of chemotherapy regimens for advanced breast cancer. However, due to heterogeneity among the studies above, further research is warranted to confirm the efficacy of a specific chemotherapy regimen over another. *High-dose chemotherapy (Four studies)* • A systematic review was identified which indicated that overall survival of metastatic breast cancer was not significantly improved by high-dose chemotherapy.[32] • One RCT compared progression free survival and overall	

	survival in women with metastatic breast cancer receiving high-dose chemotherapy plus autologous stem-cell (HDCT) transplantation.[33] The results of the study indicated that HDCT did not improve overall survival in women with metastatic breast cancer when used as consolidation after response to induction chemotherapy. • One systematic review was identified which compared the effectiveness of high-dose chemotherapy and autologous bone marrow or stem cell transplantation with conventional chemotherapy for women with metastatic breast cancer.[34] The review concluded that although there is evidence that high-dose chemotherapy and autograft significantly improved event-free survival compared to conventional chemotherapy there is no significant evidence of benefit in overall survival. • An RCT was identified which assessed the impact of first-line high-dose chemotherapy (cyclophosphamide and thiotepa) with stem cell support on overall survival, disease free survival and response rate in patients with metastatic breast	

	cancer.[35] The results of the study indicated that treatment improved disease free survival but not overall survival. In summary, some new evidence was identified relating to high-dose chemotherapy. No recommendations are currently provided in the guideline relating to high-dose chemotherapy. However, due to heterogeneity among the identified new evidence it would be pertinent to await further evidence before considering for inclusion in the guideline. *Monotherapy versus combination therapy (Two studies)* • One systematic review was identified which compared single agent chemotherapy with combination therapy for the treatment of metastatic breast cancer concluding that combination chemotherapy regimens showed a significant advantage for survival, tumour response and time to progression although toxicity was higher.[36] • In addition, a systematic review assessed the effects of	

	adding chemotherapy drugs to an established regimen in women with metastatic breast cancer.[37] The addition of chemotherapy drugs led to an advantage for tumour response but no difference in survival time or time to progression. The identified new evidence does not invalidate the current guideline recommendation which states: • Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. *Treatment duration (One study)* • One systematic review evaluated the effect of different first-line chemotherapy durations in patients with metastatic breast cancer indicating that longer first-line chemotherapy duration leads to marginally longer overall survival and longer	

	progression free survival.[38] *Adverse effects (One study)* • One systematic review evaluated the risk of early and late cardiotoxicity of anthracycline agents in patients treated for breast (mainly advanced) and other cancers however insufficient robust evidence was identified.[39] <u>Chemotherapy – monotherapies (12 studies)</u> *Docetaxel (Four studies)* • Two RCTs were identified which compared weekly docetaxel versus 3-weekly docetaxel for metastatic breast cancer concluding that the 3-weekly schedule was preferable.[40,41] • An additional RCT compared weekly versus every three weeks docetaxel schedules among patients with metastatic breast cancer although no difference was observed between the two regimens in any measured outcomes.[42]	

	• One RCT aimed to determine whether concomitant administration of docetaxel plus zosuquidar.3HC1 can prolong progression-free survival in patients with metastatic breast cancer.[43] The study concluded that the treatment combination is safe but there is no difference in progression free survival or overall survival. In summary, the identified new evidence does not invalidate the current guideline recommendation that single-agent docetaxel should be used as a first-line chemotherapy. Two studies indicated that a 3-weekly schedule of docetaxel is preferable however, further research is warranted to confirm these results. *Paclitaxel (Three studies)* • Three studies were identified relating to paclitaxel for advanced breast cancer. One RCT concluded albumin-bound paclitaxel (nab-paclitaxel) had greater efficacy compared with solvent-based paclitaxel (sb-paclitaxel) in patients with	

	metastatic breast cancer.[44] • A meta-analysis concluded that a weekly regimen of paclitaxel gave overall survival advantages compared with a standard every three weeks regimen.[45] • The results of one RCT indicated that a 96-hour paclitaxel infusion schedule did not significantly improve response or time to progression.[46] Paclitaxel is not currently recommended in the guideline except in combination with gemcitabine: • Gemcitabine in combination with paclitaxel, within its licensed indication, is recommended as an option for the treatment of metastatic breast cancer only when docetaxel monotherapy or docetaxel plus capecitabine are also considered appropriate. However, the new literature is currently too heterogeneous, including comparisons of different treatment regimens, to make a	

	conclusion about the efficacy of paclitaxel as a monotherapy for advanced breast cancer. *Ixabepilone (Two studies)* • Two systematic reviews were identified which suggested that ixabepilone could be a potential treatment option for metastatic breast cancer.[47,48] This treatment is not currently licensed for breast cancer. However, Ixabepilone for breast cancer (locally advanced or advanced) has been referred for a single Technology Appraisal which may have an impact on the guideline recommendations in the future. *Doxorubicin (One study)* • A post-hoc analysis of an RCT was identified which aimed to develop a risk predication model for neutropenic complications during chemotherapy with doxorubicin.[49] The study concluded that use of the model may improve patient	

	care by targeting preventative therapies to patients most likely to experience neutropenic complications during chemotherapy. A related clinical guideline is currently in progress: Neutropenic sepsis: Prevention and management of neutropenic sepsis in cancer patients (expected date of publication: August 2012). *Everolimus (One study)* • The efficacy and safety of oral everolimus (10 mg daily versus 70 mg weekly) in minimally pretreated patients with metastatic breast cancer was investigated in an RCT.[50] The response rate with daily therapy was 12% compared with 0% for weekly therapy. *Eribulin (One study)* • Overall survival in patients with metastatic breast cancer receiving eribulin compared with currently available treatments was assessed in an RCT.[51] The results of the	

	study indicated that overall survival was improved in women receiving eribulin. Currently there is an ongoing Technology Appraisal 'Eribulin for the treatment of locally advanced or metastatic breast cancer' (publication date TBC) which may have an impact on the guideline recommendations in the future. <u>Chemotherapy – combined therapies (16 studies)</u> *Capecitabine and ixabepilone (Three studies)* • Three studies were identified which evaluated the efficacy of ixabepilone combined with capecitabine for metastatic breast cancer with variable results obtained.[52,53,54] *Doxorubicin and docetaxel (Three studies)* • One RCT was identified which assessed maintenance therapy with pegylated liposomal doxorubicin (PLD) after induction chemotherapy (doxorubicin plus docetaxel) in	

	patients with metastatic breast cancer.[55] Time to progression was improved in the PLD group although overall survival was not significantly prolonged. Similar results were obtained in a second RCT.[56] • One RCT compared the toxicity and efficacy of weekly versus 3-weekly administration of docetaxel in combination with doxorubicin.[57] The study concluded that both treatment regimens were feasible although the 3-weekly application would be preferable. *Gemcitabine and docetaxel (Three studies)* • Three studies evaluated the efficacy of gemcitabine plus docetaxel in women with advanced breast cancer. Although different treatment regimens were used, no study observed statistically significant differences in time to disease progression or survival compared with the control group.[58,59,60]	

	Paclitaxel and epirubicin (Two studies) • The efficacy and safety of two treatment regimens including epirubicin and paclitaxel for patients with metastatic breast cancer was assessed in an RCT.[61] The response rates and progression free survival for both treatment regimens were similar. • One RCT compared the effect on health-related quality of life of epirubicin plus paclitaxel (ET) versus epirubicin, paclitaxel and capecitabine (TEX) in women with metastatic breast cancer.[62] At the nine month assessment, the TEX group scored significantly higher for global quality of life and physical functioning. *Gemcitabine and paclitaxel (One study)* • One RCT was identified which compared the efficacy of gemcitabine plus paclitaxel versus paclitaxel alone after prior anthracycline treatment in patients with advanced breast cancer.[63] Median survival and time to progression was longer	

	in the combination group although adverse events were more common compared with control. *Vinorelbine and capecitabine (One study)* • The efficacy and safety of sequential versus simultaneous use of vinorelbine and capecitabine at the same dosage as first-line therapy in metastatic breast cancer was assessed in an RCT.[64] An improvement in clinical benefit rate was observed in the simultaneous group but this did not translate into long-term benefits such as progression free survival and overall survival. *Capecitabine and enzastaurin (One study)* • One RCT evaluated the efficacy of enzastaurin in combination with capecitabine in patients with metastatic or recurrent breast cancer.[65] No progression free survival benefit was observed with combined therapy whilst median overall survival was lower compared with the control group.	

	Vinorelbine and gemcitabine (One study) • One RCT was identified which compared gemcitabine and vinorelbine versus gemcitabine until disease progression followed by vinorelbine monotherapy in patients with metastatic breast cancer.[66] The study concluded that both treatment regimens were comparable in terms of efficacy and toxicity. *Vinorelbine and chronomodulated 5-fluorouracil (One study)* • An RCT was identified which aimed to determine the least toxic time of vinorelbine administration in patients with metastatic breast cancer however, no recommendation on optimal time of administration could be made.[67] In summary, new literature was identified relating to combined therapy for advanced breast cancer. The guideline recommendation currently states: consider using combination chemotherapy to treat	

	patients with advanced breast cancer for whom a greater probability of response is important and who understand and are likely to tolerate the additional toxicity. However, a meta-analysis is necessary to support the use a certain combination of chemotherapy over other combinations. <u>Chemotherapy versus chemotherapy (21 studies)</u> *Comparisons of mixed chemotherapy regimens (Five studies)* • One RCT compared four treatment regimens for advanced breast cancer.[68] The study concluded that incorporation of docetaxel into anthracycline-based therapy resulted in an improvement in disease free survival and that sequential administration may provide more benefit compared with concurrent. • One RCT carried out comparisons between doxorubicin plus cyclophosphamide, docetaxel and alternating cyclophosphamide and docetaxel as first-line chemotherapy for metastatic breast cancer however, no difference in time to	

	survival was observed between the three treatment arms.[69] • One RCT comparing anthracycline-based adjuvant chemotherapy (control arm) to anthracycline-docetaxel-based sequential or concurrent chemotherapy concluding that there is no evidence that adjuvant docetaxel treatment is associated with an increased frequency of CNS relapse.[70] • A meta-analysis was identified which aimed to determine the efficacy of taxanes alone or in combination with anthracyclines as first-line therapy for metastatic breast cancer.[71] • The objective response to biweekly gemcitabine/paclitaxel, gemcitabine/carboplatin and gemcitabine/cisplatin as first line treatment for metastatic breast cancer was assessed in an RCT with comparable activity and tolerability observed.[72] In summary, the above studies evaluate chemotherapy regimens for treatment of advanced breast cancer. However, as the studies compared different combinations of chemotherapies (and each	

	different combinations was only supported by one study), further evidence is required to further assess the choice of one chemotherapy regimen over another. *Paclitaxel versus docetaxel (Three studies)* • One RCT assessed the efficacy and tolerability of weekly paclitaxel compared with weekly docetaxel in metastatic breast cancer patients concluding that administration of either treatment could be considered.[73] Conversely, the results of one RCT indicated that weekly nab-paclitaxel demonstrated superior efficacy and safety compared with docetaxel.[74] • The tolerability of weekly paclitaxel or docetaxel combined with non-pegylated liposomal anthracycline in first-line metastatic breast cancer patients was evaluated in an RCT.[75] The study concluded that combined weekly administration of taxane and non-pegylated liposomal anthracycline is well tolerated in this population.	

	Docetaxel and gemcitabine versus docetaxel and capecitabine (Two studies) • The efficacy and safety of docetaxel and gemcitabine compared with docetaxel and capecitabine in patients with advanced breast cancer was assessed in two RCTs with both studies concluding that the treatment regimens have similar efficacy.[76,77] *Capecitabine versus vinorelbine (One study)* • One RCT was identified which assessed the safety and efficacy of capecitabine compared with vinorelbine in patients with metastatic breast cancer following prior treatment with taxanes and anthracyclines.[78] The results of the study indicated that both treatments had comparable efficacy. *Docetaxel versus vinorelbine (One study)* • The efficacy of weekly vinorelbine compared with weekly	

	docetaxel in patients with anthracycline-pretreated metastatic breast cancer was assessed in an RCT.[79] The study concluded that docetaxel demonstrated marginally better activity but did not improve time to progression compared with vinorelbine. *Epirubicin and cyclophosphamide versus epirubicin and docetaxel (One study)* • One RCT compared the safety and efficacy of epirubicin and cyclophosphamide with epirubicin and docetaxel in patients with metastatic breast cancer.[80] The results of the study indicated that both treatments had comparable efficacy. *Doxorubicin versus docetaxel (One study)* • The efficacy and safety of doxorubicin compared with docetaxel as first-line treatment for patients with metastatic breast cancer was evaluated in an RCT.[81] The results of the study indicated that both treatments had comparable efficacy	

	and were both well tolerated. *Doxorubicin and docetaxel versus doxorubicin and cyclophosphamide (One study)* • The efficacy of doxorubicin and cyclophosphamide compared with doxorubicin and docetaxel in women with invasive breast cancer that had metastasised was assessed in an RCT.[82] The results of the study indicated that both treatments had comparable efficacy although doxorubicin and docetaxel treatment was associated with more toxicity. *Doxorubicin and docetaxel versus doxorubicin and paclitaxel (One study)* • One RCT was identified which compared doxorubicin and docetaxel with doxorubicin and paclitaxel in patients with metastatic breast cancer.[83] The results of the study indicated that both treatments had comparable efficacy although toxicity profiles differed between the two groups.	

	Doxorubicin and paclitaxel versus fluorouracil, doxorubicin and cyclophosphamide (One study) • The efficacy of doxorubicin and paclitaxel versus fluorouracil, doxorubicin and cyclophosphamide in women with advanced breast cancer was assessed through post-hoc analysis of an RCT.[84] The results of the study indicated that time to progression and overall survival was longer in the group receiving doxorubicin and paclitaxel therapy. *Docetaxel and epirubicin versus docetaxel and capecitabine (One study)* • One RCT was identified which compared docetaxel and epirubicin with docetaxel and capecitabine in women with advanced breast cancer.[85] The results of the study indicated that both treatments had comparable efficacy although toxicity profiles differed between the two groups.	

	Epirubicin/vinorelbine versus pegylated liposomal doxorubicin/vinorelbine (One study) • One RCT was identified which investigated the efficacy and tolerability of epirubicin plus vinorelbine compared with pegylated liposomal doxorubicin plus vinorelbine in patients with advanced breast cancer.[86] The study concluded that both treatment regimens were active with acceptable tolerability. *Gemcitabine and vinorelbine versus gemcitabine and cisplatin versus gemcitabine and capecitabine (One study)* • An RCT was identified which compared three treatment regimens (Gemcitabine plus vinorelbine; gemcitabine plus cisplatin and gemcitabine plus capecitabine) in patients with pretreated metastatic breast cancer.[87] The study concluded that all treatment regimens evaluated were active with acceptable tolerability.	

	Paclitaxel and carboplatin versus doxorubicin and paclitaxel versus paclitaxel (One study) • One RCT evaluated the effectiveness of paclitaxel plus carboplatin compared with docetaxel plus gemcitabine or paclitaxel alone in patients with metastatic breast cancer.[88] No differences in time to progression or quality of life between the three treatment methods were observed although cost analysis favoured paclitaxel. In summary, the above studies evaluated different chemotherapy regimens for treatment of advanced breast cancer. However, as the studies compared different combinations of chemotherapies (and each different combination was only supported by one or two studies with inconclusive summaries), further evidence is required to further assess the choice of one chemotherapy regimen over another. <u>Chemotherapy – management of chemotherapy-related adverse</u>	

	effects (Two studies) *Epoetin therapy (Two studies)* • One RCT (BRAVE study) was identified which evaluated whether epoetin beta could improve survival in patients with metastatic breast cancer.[89] The results of the study indicated that median iron levels increased in the treatment group however no difference in overall survival, compared with control, was observed. Thromboembolic events were higher in the epoetin group. A post-hoc analysis of the BRAVE study concluded that antithrombotic therapy may have the potential to reduce the risk of thrombovascular events under epoetin therapy.[90] **Summary** New literature was identified relating to paclitaxel, doxorubicin, ixabepilone and eribulin as treatment for advanced breast cancer. However, heterogeneity across studies in terms of treatment regimens and reported results was apparent. For other treatments	

	only single trials were identified therefore further study is warranted to confirm the results obtained. As such, no conclusive new literature was identified which would change the direction of current guideline recommendations. Relevant Technology Appraisals are in development which may have an impact on the guideline recommendations in the future. Limited evidence was identified focusing on gemcitabine. However, the recommendation relating to gemcitabine, which was incorporated from TA116, is not likely to change as the Technology Appraisal has been placed on the static list.	
Clinical area 3: Systemic disease-modifying therapy (biological therapy)		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the most effective biological treatment for (1) women and (2) men with metastatic breast cancer?	Through an assessment of abstracts from the high-level RCT search, 16 studies relevant to the clinical questions were identified. <u>Biological therapy – monotherapies (14 studies)</u> *Lapatinib (Five studies)*	This section of the guideline needs to cross refer to a new technology appraisal that was previously not

Relevant section of the guideline and recommendations Chapter 4: Systemic disease-modifying therapy - biological therapy	• Five studies were identified focusing on the clinical efficacy of lapatinib as treatment for advanced breast cancer.[91,92,93,94,95] Currently there are three Technology Appraisals in progress (two currently suspended and one with publication date TBC) relating to lapatinib: ○ Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. Status: publication date TBC. ○ Lapatinib for breast cancer (first line use in advanced or metastatic hormone-sensitive breast cancer). Status: currently suspended. ○ Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer). Status: currently suspended. *Bevacizumab (Three studies)*	mentioned in the guideline - TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011.

	• Three studies were identified relating to bevacizumab for advanced breast cancer. [96,97 ,98] There are currently two Technology Appraisals relating to bevacizumab (one published and one in progress) which review the use of bevacizumab in combination with chemotherapy for the treatment of metastatic breast cancer:
	  ○ TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011.
	  ○ Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer. Status: publication date August 2012.
	
	Trastuzumab (Two studies)
	• Through the review of the guideline two studies were identified relating to trastuzumab for advanced breast cancer.[99,100] Within the guideline, the recommendations on the use of trastuzumab are covered by TA34 (2002)	

	however, a review of this guidance has been planned into the Technology Appraisal work programme and therefore may have an impact on guideline recommendations in the future. *Erlotinib (One study)* • The efficacy and safety or erlotinib in advanced breast cancer was evaluated in a cohort study however, the results indicated that this treatment had minimal activity in unselected previously treated women with advanced breast cancer.[101] *Adecatumumab (One study)* • One RCT was identified which compared two doses (high-dose versus low-dose) of adecatumumab in patients with metastatic breast cancer.[102] The results of the study indicated that the probability of tumour progression was lower in patients receiving the high-dose therapy although adverse events were higher in this group.	

	Pertuzumab (One study) • An RCT compared two doses of pertuzumab in patients with human epidermal growth factor receptor 2 (HER2) –negative metastatic breast cancer.[103] Limited efficacy of pertuzumab was observed. *Pan-ErbB receptor tyrosine-kinase inhibitor CI-1033 (One study)* • The efficacy and safety of three different doses of a pan-ErbB receptor tyrosine-kinase inhibitor in metastatic breast cancer was evaluated in an RCT.[104] The results of the study indicated that there was no clinically meaningful activity associated with treatment in heavily pretreated patients with metastatic breast cancer expressing more than one ErbB receptor, <u>Biological therapy – combined therapies (Two studies)</u> *Pertuzumab and trastuzumab (One study)*	

	• One single-arm, open-label trial was identified which evaluated the efficacy and safety of pertuzumab in combination with trastuzumab in advanced breast cancer.[105] The results of the study indicated that the objective response rate was 24.2% and the clinical benefit rate was 50% whilst combination treatment was well tolerated. *Lapatinib and trastuzumab (One study)* • One RCT was identified which compared the efficacy of lapatinib alone or in combination with trastuzumab in women with ErbB2-positive metastatic breast cancer.[106] The results of the study indicated that combination therapy was beneficial compared to lapatinib alone for progression free survival whilst a trend towards improved overall survival was also observed. **Summary** In summary, for some treatments only single trials were identified	

	therefore further study is warranted to confirm the results obtained. In addition, new literature was identified relating to lapatinib, bevacizumab and trastuzumab as treatment for advanced breast cancer. In terms of bevacizumab, the guideline needs to cross refer to the new technology appraisal (TA214) that was previously not mentioned in the guideline. In addition, other relevant Technology Appraisals are in development relating to lapatinib and trastuzumab which may have an impact on the guideline recommendations in the future.	
Clinical area 4: Systemic disease-modifying therapy (combination therapies and comparisons between therapies)		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the most effective treatment for (1) women and (2) men with metastatic breast cancer?	Through an assessment of abstracts from the high-level RCT search, 37 studies relevant to the clinical questions were identified. <u>Combined chemotherapy and biological therapy (24 studies)</u> *Bevacizumab plus paclitaxel (Five studies); bevacizumab plus*	The guideline needs to cross refer to a new technology appraisal that was previously not mentioned in the

Relevant section of guideline Chapter 4: Systemic disease-modifying therapy	*various chemotherapy regimens (Two studies) and bevacizumab plus docetaxel (Three studies)* • Five studies were identified which evaluated the efficacy of bevacizumab combined with paclitaxel for metastatic breast cancer.[107,108,109,110,111] The treatment protocols differed between the studies and variable results were reported. The efficacy and safety of bevacizumab combined with docetaxel was evaluated in three studies.[112,113,114] In addition, two studies evaluated the efficacy of bevacizumab in combination with various chemotherapy regimens for advanced breast cancer.[115,116] However, a Technology Appraisal has recently been published which reviews the use of bevacizumab in combination with a taxane for the treatment of metastatic breast cancer whilst a Technology Appraisal on bevacizumab in combination with capecitabine for metastatic breast cancer is in progress: ○ TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer,	guideline - TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011.

	2011. ○ Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer. Expected issue date: August 2012. *Lapatinib and capecitabine (Four studies)* • Three RCTs and a systematic review were identified which indicated a beneficial effect of lapatinib plus capecitabine versus capecitabine alone on the reported outcomes in patients with advanced breast cancer.[117,118,119,120] Ongoing Technology Appraisals on lapatinib are in development which may have an impact on the guideline recommendations in the future. *Trastuzumab and capecitabine (Three studies)* • One study was identified where patients with HER2-positive advanced breast cancer that progressed during treatment with trastuzumab were randomly assigned to receive	

	capecitabine alone or in combination with trastuzumab.[121] An improvement in overall response and time to progression was observed in the group continuing with trastuzumab plus capecitabine. A follow-up analysis did not demonstrate a significant survival benefit for treatment beyond progression with trastuzumab.[122] • One RCT was identified which evaluated trastuzumab and docetaxel with or without capecitabine as first-line combination therapy for HER2-positive advanced breast cancer concluding that treatment with trastuzumab, docetaxel and capecitabine was an effective and feasible first-line therapy.[123] *Trastuzumab and docetaxel (Two studies)* • One RCT was identified which compared trastuzumab and docetaxel with sequential therapy of single-agent trastuzumab followed at disease progression by docetaxel alone for metastatic breast cancer.[124] Progression free	

	survival was similar in both groups whilst overall survival was nonsignificantly shorter in the group receiving sequential therapy of single-agent trastuzumab followed by docetaxel. • One RCT concluded that trastuzumab and docetaxel combination therapy as first-line treatment for metastatic breast cancer was superior to trastuzumab monotherapy followed by docetaxel at disease progression.[125] *Trastuzumab and paclitaxel (One study)* • One RCT was identified which compared treatment with paclitaxel weekly or every three weeks for metastatic breast cancer whilst after the first 171 patients all HER2 positive patients received trastuzumab in addition to paclitaxel.[126] The results of the study indicated that, in the combined sample, weekly paclitaxel was superior to every three weeks administration. *Lapatinib and paclitaxel (One study)*	

	• The efficacy of lapatinib plus paclitaxel as first-line treatment for metastatic breast cancer was assessed in an RCT.[127] Patients with HER2-negative metastatic breast cancer did not benefit from the addition of lapatinib however improved clinical outcomes were observed in HER2-positive patients. *Docetaxel and axitinib (One study)* • One RCT assessed the safety and efficacy of axitinib plus docetaxel in metastatic breast cancer.[128] No significant difference in time to progression compared with control was observed. *Trastuzumab, epirubicin and cyclophosphamide (One study)* • One RCT was identified which assessed the cardiac safety and efficacy of trastuzumab plus cyclophosphamide and epirubicin for HER2-positive metastatic breast cancer indicating this may be a promising treatment regimen in this population.[129]	

	Iniparib, gemcitabine and carboplatin (One study) • One RCT was identified which compared the efficacy and safety of gemcitabine and carboplatin with or without iniparib in patients with metastatic breast cancer.[130] The results of the study indicated that the addition of iniparib to gemcitabine and carboplatin improved the rate of clinical benefit, the rate of overall response and the median overall survival. In summary, no recommendations are currently included in the guideline relating to combined biological therapy and chemotherapy. However, one relevant Technology Appraisal has been published (TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011) whilst other Technology Appraisals are in development (relating to bevacizumab and trastuzumab) which may have an impact on the guideline recommendations in the future.	

	<u>Combined biological therapy and endocrine therapy (Six studies)</u> *Lapatinib and letrozole (Three studies)* • Three RCTs were identified which indicated enhanced progression free survival in patients with advanced breast cancer treated with letrozole plus lapatinib.[131,132,133] *Trastuzumab and anastrazole (One study)* • One RCT was identified which compared the efficacy of anastrazole with or without trastuzumab in postmenopausal women with HER2/hormone receptor copositive metastatic breast cancer.[134] The results of the study indicated that combined therapy improved outcomes for this patient population although adverse events were more frequent. *Gefitinib and anastrazole (One study)* • One RCT was identified which assessed the efficacy and tolerability of anastrazole combined with gefitinib in women with HER2-positive metastatic breast cancer.[135] Combination	

	therapy was associated with improved progression free survival and was well tolerated. *Tipifarnib and letrozole (One study)* • One RCT evaluated the clinical efficacy of letrozole combined with tipifarnib versus letrozole plus placebo in patients with advanced breast cancer.[136] The results of the study indicated no difference in response duration, time to disease progression or survival. In summary, no recommendations are currently included in the guideline relating to combined biological therapy and endocrine therapy. However, there is currently a related Technology Appraisal in development: Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2 (publication date TBC). This Technology Appraisal may have an impact on the guideline recommendations in the future.	

	<u>Combined chemotherapy, biological therapy and endocrine therapy (One study)</u> *HER2-targeted agents plus chemotherapy and endocrine therapy (One study)* • A meta-analysis evaluated the efficacy of HER2-targeted therapy in addition to standard therapy (hormone or chemotherapy) in patients with metastatic breast cancer.[137] The meta-analysis concluded that addition of HER2-targeted agents improved overall survival, time to progression and progression free survival. <u>Chemotherapy versus biological therapy (Three studies)</u> *Sunitinib versus capecitabine (One study)* • One RCT was identified which compared the efficacy of sunitinib with capecitabine with the study concluding that sunitinib should not be used as monotherapy for advanced breast cancer.[138]	

	Sunitinib plus paclitaxel versus bevacizumab plus paclitaxel (One study) • One RCT compared progression free survival following treatment with sunitinib plus paclitaxel versus bevacizumab plus paclitaxel for advanced breast cancer.[139] The results of the study indicated that the sunitinib plus paclitaxel treatment regimen was clinically inferior to bevacizumab plus paclitaxel. *Docetaxel and trastuzumab versus docetaxel, carboplatin and trastuzumab (One study)* • One RCT was identified which compared the efficacy of trastuzumab plus docetaxel versus docetaxel, carboplatin and trastuzumab for metastatic breast cancer.[140] Addition of carboplatin did not enhance the antitumour activity of trastuzumab and docetaxel. Two in progress Technology Appraisals on sunitinib were identified	

	which may have an impact on the guideline recommendations in the future: • Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer. Status: currently suspended. • Sunitinib in combination with a taxane within its licensed indication for the first line treatment of advanced and/or metastatic breast cancer. Status: currently suspended. <u>Chemotherapy versus endocrine therapy (One study)</u> *Chemotherapy alone versus endocrine therapy alone (One study)* • A systematic review was identified which evaluated whether starting treatment with chemotherapy or endocrine therapy for metastatic breast cancer had a more beneficial effect on outcomes.[141] The review concluded that first-line treatment with endocrine therapy is recommended for metastatic breast cancer where hormone receptors are present.	

	Vaccines (Two studies) • One RCT was identified which evaluated time to progression and overall survival in women with advanced breast cancer who received a sialyl-TN (STn) keyhole limpet hemocyanin (KLH) vaccine.[142] The results of the study indicated that the vaccine was well-tolerated however, no overall benefit in time to progression or overall survival was observed. • The immunogenicity and safety of a NeuGcGM3 based cancer vaccine in patients with advanced breast cancer who had received first line chemotherapy was investigated in an RCT.[143] The study concluded that there was a trend towards a survival advantage in the vaccine treated group however, further study is required. **Summary** In summary, new evidence was identified relating to combination systemic disease modifying therapy for advanced breast cancer, in particular combined chemotherapy plus biological therapy	

	(bevacizumab or lapatinib combined with chemotherapy) and combined endocrine plus biological therapy (lapatinib and letrozole). However, a Technology Appraisal has been published (TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011) whilst another is currently in development with an expected publication date of August 2012 (Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer) therefore cross-referral to these in the guideline would be warranted. In addition, relevant Technology Appraisals are in development which may have an impact on the guideline recommendations in the future. Only two studies were identified which evaluated vaccines for advanced breast cancer. Hence, more evidence is warranted before this intervention could be considered within the guideline.	
Clinical area 5: Community-based treatment and supportive care		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the role of ongoing	Through an assessment of abstracts from the high-level RCT	No conclusive new

management of advanced breast cancer patients in the community setting? **Relevant section of the guideline and its recommendations** Chapter 5: Community-based treatment and supportive care	search, seven studies relevant to the clinical question were identified. <u>Supportive care (Seven studies)</u> • An observational study involving 20 women with advanced breast cancer explored psychological reactions and coping on disease progression after first-line chemotherapy.[144] Several coping strategies were assessed including work and social support. • A systematic review identified five studies of group psychological therapies (including cognitive-behavioural or supportive-expressive) which demonstrated little evidence of benefit.[145] • A post-hoc analysis of an RCT assessing supportive-expressive group therapy was identified.[146] The study concluded that decreasing depression symptoms over the first year were associated with longer subsequent survival in this population.	evidence was identified which would invalidate current guideline recommendation(s).

	• The impact of a mobile phone-based remote monitoring, advanced symptom management system (ASyMS) on the incidence, severity and distress of chemotherapy-related symptoms was assessed in a study.[147] The results of the study indicated that reports of fatigue were lower in the intervention group. • The effect of emotionally expressive writing in women with metastatic breast cancer was evaluated in an RCT.[148] The intervention was found to be more beneficial in women who had been recently diagnosed with metastatic breast cancer. • One RCT was identified which evaluated the effect of a brief self-administered psychological intervention on the well-being of women with metastatic breast cancer and men with metastatic prostate cancer.[149] An improvement in quality of life was observed whilst compliance was good. • The feasibility and acceptability of an online peer support group intervention for women with metastatic breast cancer	

	was assessed in an RCT.[150] The results of the study indicated that reported satisfaction with the intervention was high. **<u>In summary</u>** In summary, new literature was identified focusing on a variety of supportive strategies which were generally effective however, there is currently insufficient evidence to support the choice of one intervention over another. As such, the identified new evidence is unlikely to change the direction of current guideline recommendations.	
Clinical area 6: Managing complications		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What are the best management strategies for: • Uncontrolled local disease	Through an assessment of abstracts from the high-level RCT search, 19 studies relevant to the clinical questions were identified. Management of lymphoedema was assessed through a focused search question following intelligence from the Guideline	No conclusive new evidence was identified which would invalidate current guideline

• Cancer-related fatigue • Solitary or multiple bone-metastases • Solitary or multiple brain metastases • Pain • Acute radiodermatitis? **Relevant section of the guideline and its recommendations** Chapter 6: Managing complications	Development Group, with identified literature discussed in Table 2 below. *Cancer-related fatigue (Five studies)* • One RCT evaluated the effect of a multimodal group exercise intervention, as an adjunct to conventional care, on fatigue, physical capacity, general wellbeing, physical activity, and quality of life in patients with cancer who were undergoing adjuvant chemotherapy or treatment for advanced disease.[151] A reduction in fatigue was observed although no change in quality of life occurred. • The clinical factors that may predict exercise training responses in patients with breast cancer were assessed in an RCT.[152] The results of the study indicated that patient preference, medical variables and demographic variables moderated the effects of exercise training in breast cancer patients undergoing chemotherapy. In addition, the predictors of adherence to supervised exercise training during	recommendation(s).

	chemotherapy for breast cancer were evaluated in an RCT and included disease stage, aerobic fitness and depression.[153] • A Cochrane systematic review was identified which evaluated the effectiveness of psychosocial interventions in reducing cancer related fatigue.[154] The review concluded that there is limited evidence that psychosocial interventions during cancer treatment are effective in reducing fatigue although this may be a promising intervention. • An additional Cochrane systematic review was identified which aimed to determine efficacy of pharmacological treatments on non-specific fatigue in palliative care with a focus on patients at an advanced stage of disease, including cancer.[155] The review concluded that methylphenidate for fatigue in patients suffering from advanced cancer warrants further study. The new literature on management of cancer-related fatigue is in	

	line with the current guideline recommendation that patients with advanced breast cancer should have access to an exercise programme. The literature on psychosocial and pharmacological interventions for cancer related fatigue indicates that these interventions warrant further study. *Uncontrolled local disease (One study)* • One Cochrane systematic review was identified which evaluated the evidence relating to the effects of dressings and topical agents on quality of life in people with fungating malignant wounds.[156] The review concluded that 6% miltefosine solution applied topically to people with superficial fungating breast lesions who have previously received radiotherapy, surgery, hormonal therapy or chemotherapy for their breast cancer, may slow disease progression. However, more research is needed on managing wound symptoms associated with fungating wounds.	

	In terms of uncontrolled local disease, the new literature is unlikely to change the direction of current recommendation which states that a wound care team should see all patients with fungating tumours to plan a dressing regimen and supervise management with the breast care team. *Bone metastases (Eight studies)* • The efficacy and safety of high- or reduced-dose radiotherapy combined with zoledronic acid in breast cancer patients with bone metastases was assessed in an RCT.[157] No significant differences were found in pain scores or bone scintigraphy results between the two groups indicating that reduced-dose radiotherapy produces a similar response rate to high-dose radiotherapy. • The incidence of adverse effects following administration of denosumab or intravenous bisphosphonate in patients with advanced breast cancer and bone metastases was evaluated in an RCT.[158] The results of the study indicated that patients	

	receiving denosumab had fewer adverse effects than those receiving intravenous bisphosphonate at three days and four weeks following treatment initiation. In addition, the efficacy of denosumab in breast cancer patients with bone metastases not receiving prior bisphosphonate therapy was investigated in an RCT.[159] The study concluded that denosumab appeared to reduce the risk of skeletal-related events in breast cancer patients who had not received prior bisphosphonate therapy. • An RCT was identified which compared subcutaneous denosumab with intravenous zoledronic acid or placebo in patients with breast cancer and bone metastases.[160] The results of the study indicated that denosumab was superior to zoledronic acid in delaying or preventing skeletal-related events in patients with bone metastases. • A Cochrane systematic review was identified which evaluated the effect of bisphosphonates on skeletal events and bone pain in women with early or advanced breast	

	cancer.[161] The review concluded that in women with advanced breast cancer and bone metastases, bisphosphonates reduced the risk of developing skeletal events and the skeletal event rate. • One RCT was identified which assessed the safety and efficacy of ibandronate in patients with advanced breast cancer and bone metastases.[162] The results of the study indicated that treatment with intravenous ibandronate every four weeks for 24 months significantly reduced the number of patients experiencing a skeletal event compared with placebo. • The efficacy and safety of oral odanacatib, a cathepsin K inhibitor, compared with intravenous zoledronic acid in reducing markers of bone resorption in women with breast cancer and bone metastases was evaluated in an RCT.[159] The study concluded that odanacatib was generally well tolerated and could be a potentially novel therapeutic method for treating bone metastases.	

	• A long-term follow-up of an RCT was identified which evaluated whether adding oral clodronate to postoperative adjuvant breast cancer therapy improved survival in patients with bone metastases.[163] The results of the study indicated that although a significant improvement in overall survival was maintained in the clodronate group at a median follow-up of 103 +/- 12 months, significant reductions in the incidence of bony and visceral metastases and improvement in duration of disease-free survival at 36- and 55-month follow-up periods were no longer seen with clodronate. New literature was identified which indicated a beneficial effect of bisphosphonates in patients with bone metastases which supports the current guideline recommendations. In addition, new studies suggested denosumab may also be a beneficial option for managing bone metastases. However, denosumab is currently only licensed for treatment of postmenopausal osteoporosis in women at increased risk of fractures and for treatment of bone loss associated	

	with hormone ablation in men with prostate cancer. Therefore, it would be pertinent to await further evidence, particularly on the benefits, harms and cost-effectiveness of this treatment for managing bone metastases in advanced breast cancer before including in the guideline. *Brain metastases (Three studies)* • A small-scale clinical trial evaluated the efficacy and safety profile of temozolomide using protracted low-dose and whole-brain radiotherapy (WBRT) for breast cancer patients with brain metastases.[164] The results of the study indicated that the concomitant use of WBRT and protracted low-dose temozolomide appears to be active and well-tolerated although further study is required. • The efficacy, safety and tolerability of concurrent cisplatin and vinorelbine chemotherapy and radiotherapy in patients with breast cancer and brain metastases was evaluated in a clinical trial.[165] Progression-free survival was 3.7 months and	

	overall survival was 6.5 months whilst overall toxicity was acceptable. • A clinical trial was identified which assessed the use of trastuzumab concurrently with WBRT for patients with brain metastases from human epidermal growth factor receptor-2-positive breast cancer.[166] The study concluded that although promising results were obtained further research is necessary. The new literature relating to management of brain metastases was heterogeneous with the studies suggesting that further research is warranted. As such, this new literature is unlikely to change the direction of current guideline recommendations. *Management of pain (one study)* • One RCT evaluated the effects of supportive-expressive group therapy plus education versus education-only control on pain over 12 months in women with advanced breast	

	cancer.[167] The results of the study indicated that the intervention group had less increase in the intensity of pain compared with controls but there was no difference in frequency of pain episodes or amount of constant pain. *Treatment of acute radiodermatitis (one study)* • One RCT was identified which evaluated treatment of acute radiodermatitis with an oil-in-water emulsion following radiotherapy.[168] Compared with an untreated group, some beneficial effect of an oil-in-water emulsion on stratum corneum hydration was observed. In summary, only single trials were identified relating to management of pain and acute radiodermatitis therefore further study is warranted to confirm the results obtained. **Summary** In summary, no conclusive new evidence was identified relating to	

	interventions for management of cancer related fatigue, uncontrolled local disease, bone metastases, brain metastases, pain or treatment *of* acute radiodermatitis which would invalidate current guideline recommendations.	

Table 2: Summary of articles from the focused search

Clinical area 1: Diagnosis and assessment		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What are the best investigations for (1) assessing disease extent and (2) monitoring the response to treatment, including positron emission tomography (PET), in advanced breast cancer? **Relevant section of the guideline and its recommendations** Chapter 2: Diagnosis and assessment	Through an assessment of abstracts from the high-level RCT search, 21 studies relevant to the clinical questions were identified. <u>Imaging assessment (14 studies)</u> *Comparisons between imaging strategies (Seven studies)* • One study was identified which compared the diagnostic performance of 18F-deoxyglucose (FDG)-positron emission tomography (PET), computed tomography (CT) and conventional imaging for detection of distant metastases in breast cancer.[169] The study concluded that in breast cancer, FDG-PET is superior to conventional imaging procedures for detection of distant metastases. • A systematic review was identified which evaluated the	No conclusive new evidence was identified which would invalidate current guideline recommendation(s).

	accuracy of ultrasound (US), CT, magnetic resonance imaging (MRI), scintimammography (SMM) and PET in detecting recurrent breast cancer.[170] The review concluded that MRI was the most useful imaging technique although FDG-PET could be performed in addition. • One study was identified which assessed the correlation between 18FDG-PET-CT, cancer antigen 27.29 and circulating tumour cell testing (CTC) in metastatic breast cancer.[171] The study concluded that CA 27.29 and CTC had poor sensitivity and negative predictive value to detect metastatic disease observed on PET-CT scan. • The diagnostic accuracy of diffusion-weighted whole body signal suppression (DWIBS) with skeletal scintigraphy for the detection of bone metastases was evaluated in a study.[172] The study concluded that the DWIBS is not superior to scintigraphy for staging in breast cancer. • A study was identified which compared whole body FDG-PET-CT with bone scintigraphy for the detection of bone	

	metastases in breast cancer patients.[173] The study concluded that on a lesion-basis whole-body FDG-PET-CT is more sensitive and equally specific for the detection of bone metastases compared with bone scintigraphy. • A meta-analysis compared the diagnostic value of 18FDG-PET, MRI and bone scintigraphy in detecting bone metastases in patients with breast cancer.[174] The meta-analysis concluded that MRI was better than 18FDG-PET and bone scintigraphy in diagnosis of bone metastases in patients with breast cancer on a per-patient basis. • The sensitivity of MRI and scintigraphy for detecting metastatic bone disease involving the axial skeleton was assessed in one study.[175] The study concluded that MRI was more sensitive than scintigraphy in the detection of bone metastases. In summary, due to the heterogeneity between the reported results there is currently insufficient evidence to support the choice of one	

	imaging modality over another. *Positron emission tomography fused with computed tomography (PET-CT) (Five studies)* • One study concluded that PET-CT can improve staging and alter therapeutic options in patients suspected to have breast cancer recurrence.[176] • One study was identified which compared the diagnostic value of whole-body diffusion weighted imaging (DWI) and 18Fdeoxyglucose (FDG) PET-CT for breast cancer staging.[177] However, the study concluded that further study is required to determine whether whole-body DWI could be used as an alternative to FDG PET-CT for whole-body breast cancer staging. • The accuracy of whole-body PET-CT for detecting brain metastases from non-central nervous system tumours was evaluated in a study.[178] The results of the study indicated that the sensitivity of cerebral metastases using PET-CT	

	was unsatisfactory. • One study aimed to assess the detectability of bone metastatic lesions and evaluate the correlation between 18F-fluoride uptake patterns on PET and morphologic changes on CT using integrated PET-CT.[179] The results of the study indicated that lesions with sclerotic or mixed changes or located in bone cortex alone tend to show high maximum standard uptake value (SUVmax). • One study evaluated the accuracy of 18F-fluoride PET-CT to detect bone metastases in patients with breast or prostate cancer.[180] The results indicated that 18F-fluoride PET-CT is more accurate than bone scintigraphy for detecting bone metastases from breast and prostate cancers. In summary, as the identified new evidence is variable it is unlikely to change the direction of the current guideline recommendation which states: Positron emission tomography fused with computed tomography (PET-CT) should only be used to make a new	

	diagnosis of metastases for patients with breast cancer whose imaging is suspicious but not diagnostic of metastatic disease. *Scintigraphy (One study)* • One study was identified which aimed to determine the feasibility of detecting metastatic lesions with scintigraphy using the alpha(v)beta(3)-avid imaging agent (99m)Tc-NC100692.[181] The results of the study indicated that this imaging strategy is feasible for detection of lung and brain metastases from breast cancer. *Biopsy (One study)* • One study evaluated whether confirmatory tumour biopsy alters the management of breast cancer patients with distant metastases.[182] The study concluded that there can be discordance in receptor status between primary tumour and metastases, which led to altered management in 20% of cases.	

	Monitoring disease status (Seven studies) *Positron emission tomography fused with computed tomography (PET-CT) (Three studies)* • One study concluded that PET-CT is useful in staging metastatic disease and assessing response to treatment.[183] • One study was identified which indicated that 18F-FDG PET-CT is a useful tool for monitoring in patients with bone metastases from breast cancer.[184] • A retrospective study compared morphologic and metabolic changes in bone metastases in response to systemic therapy in patients with metastatic breast cancer with integrated PET-CT.[185] The study concluded that a decrease in SUV after treatment was an independent predictor of response duration in patients with bone metastases. Two studies indicated that PET-CT is useful in monitoring disease status which differs to the current guideline recommendation which	

	states that PET-CT should not be used to monitor advanced breast cancer. However, further evidence is required comparing PET-CT with other imaging modalities for monitoring disease status to determine whether imaging with PET-CT improves management. *Carcinoembryonic antigen (CEA) and cancer antigen (CA) 15-3 (Three studies)* • The correlation between carcinoembryonic antigen (CEA) and cancer antigen (CA) 15-3 and imaging of the effectiveness of chemotherapy for metastatic breast cancer was assessed in a retrospective study.[186] The study concluded that CEA and CA 15-3 could be used as potential tools to monitor treatment response. • One study indicated the usefulness of CA15-3 kinetics in monitoring chemotherapy response in patients with metastatic breast cancer.[187] • One study was identified which compared a bone scan with CA15-3 titres in patients with breast cancer for evaluation of	

	bone metastases.[188] The results of the study indicated that the mean level of CA15-3 was higher in patients with bone metastases than those without but there was no significant relation between serum CA15-3 levels and the extent of bone metastases. Further study is warranted. New evidence was identified relating to the use of carcinoembryonic antigen and cancer antigen 15-3 in monitoring disease status, however, it would be pertinent to await further evidence before this is considered within the guideline. *Comparisons between imaging strategies (One study)* • The role of PET-CT, compared with ultrasound and MRI, in evaluating the response to neoadjuvant chemotherapy in advanced breast cancer was evaluated in one study.[189] The study concluded that MRI was superior to PET-CT and ultrasound in monitoring the effect of neoadjuvant chemotherapy in advanced breast cancer.	

	Summary In summary, new literature was identified relating to diagnosis and assessment of advanced breast cancer however, due to the heterogeneity between the reported results there is currently insufficient evidence to support the choice of one imaging modality over another. New evidence was identified relating to the use of carcinoembryonic antigen and cancer antigen 15-3 in monitoring disease status however, it would be pertinent to await further evidence before this is considered within the guideline.	
Clinical area 2: Managing complications: diagnosis of lymphoedema		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the diagnostic accuracy of specific investigations to recognise lymphoedema early in patients	Through an assessment of abstracts from a focused search, three studies relevant to the clinical question were identified. The aim of this question was to determine the diagnostic accuracy	No new evidence was identified which would invalidate current guideline

early, locally advanced and advanced (metastatic) breast cancer? **Relevant section of the guideline and recommendations** Chapter 6: Managing complications - diagnosis of lymphoedema	of specific investigations to recognise lymphoedema early in patients with early, locally advanced and advanced (metastatic) breast cancer: • One study aimed to determine whether bioimpedance spectroscopy (BIS) could detect localised lymphoedema of the arm and to compare BIS measurements with equivalent measures of limb volume by perometry.[190] The study indicated that BIS can be used for localised measurement of lymphoedema. BIS is more sensitive to localised lymphoedema than perometry because it is specific to extracellular fluid. This warrants further investigation. • The second study evaluated circumference measurement (CM) and water displacement (WD) for volume measurements (VM) of the breast cancer-related lymphedema (BCRL) arm and the contralateral arm, comparing the results with regional dual energy X-ray absorptiometry (DXA).[191] DXA is superior in repeatability when compared to CM and WD for VM, especially for the	recommendation(s).

	BCRL arm but also the contralateral arm. • Lastly, one study compared diagnostic accuracy of measures of breast cancer-related lymphoedema (BCRL).[192] The results of the study support the use of bioimpedance spectroscopy in the assessment of existing BCRL. The study also indicated that refining diagnostic cutoff values may improve accuracy of diagnosis and warrants further investigation. **Summary** In summary, two studies showed bioimpedance spectroscopy (BIS) to be effective in detecting breast cancer-related lymphoedema (BCRL) but warrant further investigation. One study indicated that circumference measurement (CM) and water displacement (WD) may not be effective compared to X-ray absorptiometry (DXA). The identified new evidence does not currently support the use of one diagnostic tool over another for recognising lymphoedema early in patients with early, locally advanced or advanced (metastatic)	

	breast cancer.	
Clinical area 3: Managing complications: management of lymphoedema		
Clinical question	**Summary of evidence**	**Relevance to guideline recommendations**
Q: What is the best management strategy of lymphoedema? **Relevant section of the guideline and recommendations** Chapter 6: Managing complications - management of lymphoedema	Through an assessment of abstracts from a focused search, 20 studies relevant to the clinical question were identified. <u>Systematic reviews (Four studies)</u> • A systematic review was identified which assessed the evidence relating to management of secondary lymphoedema following breast cancer.[193] The review indicated that beneficial treatments include physiotherapy, exercise and complex decongestive therapy. • One systematic review concluded that combined physical therapy is an effective therapy for breast cancer-related lymphoedema although further research is required to	Potential new evidence identified on exercise in patients with breast cancer-related lymphoedema.

	determine the effectiveness of the individual components of the therapy.[194] • The effects and harms of physiotherapy methods and other treatment practices for lymphoedema in breast cancer patients was assessed in a systematic review.[195] The review concluded that evidence on physiotherapy methods was limited although compression bandages seemed to be beneficial in reducing lymphoedema. • A systematic review of physiotherapy treatments for breast cancer-related lymphoedema concluded that better results are obtained with combined treatments.[196] Complex decongestive therapy combined with pneumatic compression was found to demonstrate efficacy. The systematic reviews showed some benefit of using physiotherapy, compression bandage, exercise, and complex decongestive therapy combined with pneumatic compression but further evaluations are required to validate these interventions.	

	<u>Compression therapy (Six studies)</u> *Bandaging (Two studies)* • A randomised comparative study evaluated whether there is a difference between low and high pressure bandaging in volume reduction for management of breast cancer-related arm lymphoedema.[197] No statistically significant changes in volume were observed between the two groups in the first 24 hours after application although the low pressure bandages were better tolerated. • One RCT was identified which compared alginate semi-rigid bandaging with conventional lymphologic-multilayered low-stretch bandaging for breast cancer-related lymphoedema.[198] The study concluded that alginate bandages are a good alternative to conventional bandaging. *Compression hosiery (Four studies)* • One small RCT compared the efficacy of autologous stem	

	cells in the treatment of postmastectomy lymphoedema with decongestive treatment with compression sleeves.[199] An improvement in the volume of lymphoedema was observed in both groups. • The effect of different intermittent pneumatic compression protocols (in particular, cycle time and number of sleeve chambers) on lymphoedema volume reduction was assessed in an RCT.[200] The study concluded that this is an effective method of reducing lymphoedema volume reduction regardless of the protocol used. • One systematic review was identified which evaluated the use of compression pumps for treatment of breast cancer-related upper extremity lymphoedema.[201] The review concluded that there is no evidence to suggest that treatment with an intermittent compression pump is more beneficial than education about arm care and hygiene. • One RCT was identified which compared decongestive lymphatic therapy combined with pneumatic compression	

	with Kinesio tape (K-tape) combined with pneumatic compression for breast cancer-related lymphoedema.[202] No significant differences between groups were observed for any measured outcomes. Some studies showed that alginate semi-rigid bandaging, autologous stem cells, and pneumatic compression protocols showed some effectiveness but further validation is required. Decongestive lymphatic therapy combined with pneumatic compression, compression pumps, and low and high pressure bandaging did not show any statistical significance. <u>Therapeutic exercise (Five studies)</u> • One RCT evaluated the effect of a mixed exercise programme on lymphoedema status among women who had completed treatment for breast cancer concluding that exercise did not exacerbate the lymphoedema.[203] • The results from one RCT indicated that progressive weight	

	lifting is safe for women following breast cancer who have, or are at risk of developing, lymphoedema.[204] • The effectiveness of complex decongestive physiotherapy with and without active resistive exercise for treatment of breast cancer-related lymphoedema was evaluated in an RCT.[205] The results of the study indicated that combination therapy did not cause additional swelling, reduced arm volume and improved quality of life. • One systematic review evaluating the role of exercise in lymhoedema care concluded that evidence is available on the safety of resistance exercise without an increased risk of lymphoedema in breast cancer patients.[206] • An RCT was identified which assessed the effect of twice-weekly weight lifting in women with breast cancer-related lymphoedema.[207] The results of the study indicated that weight lifting had no significant effect on limb swelling and resulted in decreased incidence of exacerbations of lymphoedema.	

	The studies showed some effectiveness of exercise, complex decongestive physiotherapy, and weight lifting in the treatment of lymphoedema. <u>Laser therapy (Two studies)</u> • One RCT was identified which compared the efficacy of an active laser with placebo in women with breast cancer-related lymphoedema.[208] Limb volume tended to decline in both groups but significantly greater reduction was observed in the active laser group at 8 and 12 weeks. • An RCT comparing low-level laser therapy (LLLT) with no laser irradiation for managing postmastectomy lymphoedema concluded that LLLT was an effective management strategy with effects maintained at the 4 week follow-up.[209] The studies showed some effectiveness of using active laser and	

	low level laser therapies but further validation is required. <u>Complex decongestive therapy (One study)</u> • One RCT was identified which compared the efficacy of complex decongestive therapy alone or in combination with intermittent pneumatic compression for breast cancer related lymphoedema.[210] The results of the study indicated that complex decongestive therapy alone produced better results compared with combination therapy. <u>Lymphatic therapy (One study)</u> • One RCT compared aqua lymphatic therapy (ALT) with self-management therapy for management of breast cancer-related lymphoedema.[211] ALT demonstrated an immediate effect on limb volume but no long-term effect. <u>Hyperbaric oxygen therapy (One study)</u> • An RCT of hyperbaric oxygen therapy (HBO) compared with	

	best standard care for arm lymphoedema after radiotherapy for breast cancer demonstrated no beneficial effect of HBO.[212] **<u>Summary</u>** In summary, through an assessment of the abstracts it was not possible to determine if the studies addressed lymphoedema management in patients with advanced breast cancer. No conclusive new literature was identified which would invalidate the recommendations relating to the use of complex decongestive therapy and multi-layer lymphoedema bandaging for management of lymphoedema. New literature was identified focusing on the safety and benefit of exercise for breast cancer-related lymphoedema. However, taking study heterogeneity into account and that this is a small area of the guideline, this new evidence may not be significant enough to warrant updating the guideline at this point.	

324 clinical trials (publication dates unknown) were identified focusing on:

- Prognosis
- Treatment and management of advanced breast cancer (including chemotherapy, radiotherapy and biological therapy)
- Vaccine therapy
- Management of bone pain
- Management of fatigue
- Palliative care

Guideline Development Group and National Collaborating Centre perspective

A questionnaire was distributed to GDG members and the National Collaborating Centre to consult them on the need for an update of the guideline. Three responses were received with respondents highlighting relevant new literature relating to exercise in combating cancer related fatigue and lymphoedema management. This feedback contributed towards the development of the clinical questions for the focused searches.

Implementation and post publication feedback

In total 54 enquiries were received from post-publication feedback, most of which were routine. The key theme emerging from post-publication feedback was queries about systematic disease-modifying therapy for advanced breast cancer.

Feedback from the NICE implementation team indicated that there has been an increase in the volume of trastuzumab, docetaxel, vinorelbine and capecitabine packs dispensed from 2000 to 2011.

No new evidence was identified through post publication enquiries or implementation feedback that would indicate a need to update the guideline.

Relationship to other NICE guidance

The following NICE guidance is related to CG81:

Guidance	Review date
TA30: Taxanes for the treatment of breast cancer, 2001.	The TA was replaced by CG81 and no longer exists.
TA54: Guidance on the use of vinorelbine for the treatment of advanced breast cancer, 2002.	The TA was replaced by CG81 and no longer exists.
NICE cancer service guidance: Improving outcomes in breast cancer: manual update, 2002.	Review date: TBC.
TA34: The clinical effectiveness and cost effectiveness of trastuzumab for breast cancer, 2002.	Review decision: October 2009. The Institute proposed that is was appropriate for the review to go ahead.
TA62: Guidance on the use of capecitabine for the treatment of locally advanced or metastatic breast cancer, 2003.	The TA was replaced by CG81 and no longer exists.
NICE cancer service guidance: Improving supportive and palliative care for adults with cancer, 2004.	Review date: TBC.
CG14: Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care, 2004.	Review date: TBC.
CG27: Referral for suspected cancer,	Following the recent review

2005.	recommendation, an update of this guideline is currently in the process of being scheduled into the work programme.
TA116: Gemcitabine for the treatment of metastatic breast cancer, 2007.	Guidance was placed on the static list in 2009.
TA147: Bevacizumab for the first-line treatment of metastatic breast cancer, 2008.	This guidance has been replaced by TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011.
CG80: Early and locally advanced breast cancer: diagnosis and treatment, 2009.	Guideline is currently under review.
TA161: Alendronate, etidronate, risedronate, raloxifene, strontium ranelate and teriparatide for the secondary prevention of osteoporotic fragility fractures in postmenopausal women, 2011.	Review date: TBC.
TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011.	Review date: 2013.
TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011.	Review date: TBC.
Quality standard for breast cancer, 2011.	Review date: TBC.
Related NICE guidance in progress	

Clinical Guideline: Neutropenic sepsis: Prevention and management of neutropenic sepsis in cancer patients.	Publication date: August 2012.
Clinical Guideline: Osteoporosis, assessment of fracture risk and the prevention of osteoporotic fractures in individuals at high risk.	Publication date: TBC.
Technology Appraisal: Eribulin for the treatment of locally advanced or metastatic breast cancer.	Publication date: TBC.
Technology Appraisal: Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer).	Status: currently suspended.
Technology Appraisal: Lapatinib for breast cancer (first line use in advanced or metastatic hormone-sensitive breast cancer).	Status: currently suspended.
Technology Appraisal: Lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2.	Publication date: TBC.
Technology Appraisal: Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer.	Publication date: August 2012.
Technology Appraisal: Trastuzumab as monotherapy and in combination with a	Status: currently suspended.

taxane for the treatment of metastatic breast cancer (to include a review of TA34).	
Technology Appraisal: Sunitinib in combination with capecitabine within its licensed indication for the treatment of advanced and/or metastatic breast cancer.	Status: currently suspended.
Technology Appraisal: Sunitinib in combination with a taxane within its licensed indication for the first line treatment of advanced and/or metastatic breast cancer.	Status: currently suspended.
Technology Appraisal: Ixabepilone for locally advanced or metastatic breast cancer.	Status: currently suspended.

Anti-discrimination and equalities considerations

No evidence was identified to indicate that the guideline scope does not comply with anti-discrimination and equalities legislation. The original scope is inclusive of women and men with invasive adenocarcinoma of the breast of clinical stage 4 (i.e. with known metastatic disease).

Conclusion

Through the process, new literature was identified focusing on the safety and benefit of exercise for breast cancer-related lymphoedema. However, taking study heterogeneity into account and that this is a small area of the guideline, this new evidence may not be significant enough to warrant updating the guideline at this point.

Two recently published related Technology Appraisals were also identified: TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011 and TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011. Therefore, there needs to be consideration of cross-referral to the relevant Technology Appraisal guidance which has been published following publication of CG81.

Through the review of the guideline, a number of single-trial studies on various comparative and combination therapies were also identified. However, since there are a number of relevant Technology Appraisals in development and a number of Technology Appraisals that are currently suspended, it is considered to be premature to propose a decision on the need to update the current guideline at this time. Therefore, the guideline should be reviewed again in one year rather than in three years time.

3. Review recommendation

The guideline should not be considered for an update at this time but will be reviewed again in one year to enable relevant Technology Appraisals, which are due to be published in 2012, to be taken into consideration.

The guideline should cross refer to new Technology Appraisals (TA214 and TA239) that were previously not mentioned in the guideline.

Centre for Clinical Practice
13 Feb 2012

Appendix I

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