NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Centre for Clinical Practice

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

Background information

Guideline issue date: 2009

3 year review: 2012

National Collaborating Centre: Cancer

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, at the earliest opportunity, to new Technology Appraisals (TA214 and TA239) that were previously not mentioned in the guideline.

Factors influencing the decision

Literature search

1. Through an assessment of abstracts from a high-level randomised control trial (RCT) search, new evidence was identified relating 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

2. No conclusive new evidence was identified in these areas which would change the direction of current guideline recommendations.

3. However, the guideline needs to cross refer to new technology appraisals that were previously not mentioned in the guideline including 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.

4. 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

5. Potential new evidence was identified on exercise in patients with breast cancer-related lymphoedema. However, taking study heterogeneity into account and that this is a small area of the guideline, it was considered that this new evidence may not be significant enough to warrant updating the guideline at this point. No conclusive new evidence was identified in any other areas evaluated through the focused searches which would change the direction of current guideline recommendations.

6. 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 and palliative care. However, at this time it is unclear whether the ongoing clinical trials will have any impact on the guideline recommendations in the future.

Guideline Development Group and National Collaborating Centre perspective

7. 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

8. 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.

9. 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.

10. 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

11. NICE guidance related to CG81 can be viewed in Appendix 1.

Summary of Stakeholder Feedback

Review proposal put to consultees:
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.

12. In total 18 stakeholders commented on the review proposal recommendation during the two week consultation period. The table of stakeholder comments can be viewed in Appendix 2.

13. Fourteen stakeholders agreed with the review proposal and three disagreed with the review proposal. One stakeholder did not state a definitive decision.

14. The stakeholders that disagreed with the review proposal commented:
    - There is new literature on lymphoedema management that has been published in 2012. However, through an assessment of the abstract it was not possible to determine if the studies addressed lymphoedema management in patients with advanced breast cancer. This area will be examined again in the future review of the guideline.
    - Nab-paclitaxel should be considered for inclusion in the guideline. Through the review of CG81 four studies were identified relating to nab-paclitaxel. However, as the studies identified compared nab-paclitaxel with different comparators, it seems premature to consider for inclusion in the guideline at this time. This area will be examined again in the future review of the guideline.

- Management of acute radiodermatitis should be included in the guideline. However, only a single trial was identified through the review process therefore further study is warranted to confirm the results obtained. As such, it seems premature to consider for inclusion in the guideline at this time. This area will be examined again in the future review of the guideline.
- Concern that the information contained within the Technology Appraisal on fulvestrant is out of date. This information will be passed to the Technical Team responsible for TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011.

Anti-discrimination and equalities considerations

15. 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

16. 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.

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

18. 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 to enable relevant Technology Appraisals, which are due to be published in 2012, to be taken into consideration.

Relationship to quality standards

19. This guideline relates to a published quality standard on breast cancer.

20. No new evidence was identified through the review of the guideline which would impact on the published quality standard on breast cancer.

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Centre for Clinical Practice
April 2012

Appendix 1

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.
CG27: Referral for suspected cancer, 2005.	Following the recent review 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.	Guidance has been replaced by TA214: Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer, 2011.
CG41: Familial breast cancer: the classification and care of women at risk of familial breast cancer in primary, secondary and tertiary care (partial update of CG14), 2006.	An update of this guideline has been scheduled into the work programme.
CG80: Early and locally advanced breast cancer: diagnosis and treatment, 2009.	Guideline is currently under review. Expected decision date: March 2012.
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.
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: June 2012.
Technology Appraisal: Bone metastases from solid tumours – denosumab.	Publication date: June 2012.
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: June 2012.
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 taxane for the treatment of metastatic breast cancer (to include a review of TA34).	Status: currently suspended.
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	Status: currently suspended.

breast cancer.	
Technology Appraisal: Ixabepilone for locally advanced or metastatic breast cancer.	Status: currently suspended.
Related NICE quality standard	
Quality standard for breast cancer, 2011.	Review date: TBC.

Appendix 2

National Institute for Health and Clinical Excellence

Advanced Breast Cancer
Guideline Review Consultation Comments Table
13 – 27 February 2012

Stakeholder	Agree with proposal not to update?	Comments	Comments on areas excluded from original scope	Comments on equality issues	Responses
NHS Warwickshire	Yes	Agree that sensible to wait for TAs relating to advanced BC to be completed	Previous guideline has been interpreted in the West Midlands as trastuzumab can be given in combination with vinorelbine – could this combination be looked at?		Thank you for your comment. Through the review of the guideline no evidence was identified relating to trastuzumab in combination with vinorelbine. This area will be examined again in the next review of the guideline.
Pfizer Ltd	Yes	Pfizer agree with the proposed decision by NICE to postpone review of the CG81. This is the right decision as 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.	None	None	Thank you for your comment.

RCGP	Yes	Robust evidence provided	N/A	N/A	Thank you for your comment.
Department of Health		I wish to confirm that the Department of Health has no substantive comments to make regarding this consultation.			Thank you for your comment.
AstraZeneca UK Ltd	No	We would like NICE to note that Faslodex 250mg is no longer licensed in the UK.			Thank you for your comment. This information will be passed to the Technical Team responsible for TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011.
AstraZeneca UK Ltd		The information and supporting evidence relating to the fulvestrant section in the existing ABC guidelines are now out of date as the 250mg dose is no longer licensed. We strongly feel that the information and supporting evidence should be updated or redacted to accurately reflect the current licensed dosage for fulvestrant: 500mg monthly with an additional 500mg dose on day 14.			Thank you for your comment. This information will be passed to the Technical Team responsible for TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011.
AstraZeneca UK Ltd		We also feel that clarification is required in the review proposal consultation document over which the fulvestrant dose used in the referenced evidence.			Thank you very much for your comment. The process of preparing the consultation document does not include a full systematic review of the literature and as such full details of the identified studies cannot be

					confirmed. The purpose of the review is to attempt to identify where there is a significant amount of new evidence that might warrant an update of the guideline recommendations.
AstraZeneca UK Ltd		We feel that review of fulvestrant in the third and fourth line setting may more accurately reflect the needs of clinicians in the ABC setting where it is important to have further options for patients with hormonally responsive advanced breast cancer. TA239 only reviewed fulvestrant in the second line setting and the Committee agreed that a role in fulvestrant remains in the third and fourth setting.			Thank you for your comment. This information will be passed to the Technical Team responsible for TA239: Fulvestrant for the treatment of locally advanced or metastatic breast cancer, 2011.
AstraZeneca UK Ltd		The reference 1 in the review proposal consultation is document is incorrectly referenced. The lead author is Di Leo not Di LA.			Thank you for highlighting this inaccuracy. This has been noted.
GDG member	Yes	Community based treatment and supportive care: Encouraging seeing RCTs etc dealing with aspects of the above, though I fail to see how “A reduction in fatigue observed” does NOT lead to “a change in quality of life.” Diagnosis and Management of Lymphoedema: Good to see studies etc providing more			Thank you for your comment.

		information on management of Lymphoedema.			
3M Health Care	No		The update consultation document for CG81 includes discussion on recently published clinical evidence that compare treatments and preventative products for radiation associated dermatitis. This area was not included in the advice of the 2009 ABC CG81 Guideline. There is earlier work on topical treatments for radiation induced desquamation that has not had the opportunity to be reviewed as part of this guideline. In our view this distressing complication of radiation therapy is deserving of inclusion in CG81 following a review of the evidence.		Thank you for your comment. Only a single trial was identified relating to management of acute radiodermatitis therefore further study is warranted to confirm the results obtained. As such, it seems premature to propose an update of this area in the guideline at this time. This area will be examined again in the future review of the guideline.
3M Health Care	No		An update of CG81 should be undertaken		Thank you for your comment. Only a single trial

			at this time and should include a complete review of topical treatments and preventative therapies to reduce the patient impact of radiation induced dermatitis. There are several well designed studies of the effectiveness of topical treatments for radiation skin reactions that pre-date the study by Jensen MM *et al* mentioned as reference 168 in the review consultation document of CG81. A complete review of the evidence supporting practice in this distressing condition is merited in a 2012 update of CG81.		was identified relating to management of acute radiodermatitis therefore further study is warranted to confirm the results obtained. As such, it seems premature to propose an update of this area in the guideline at this time. This area will be examined again in the future review of the guideline.
3M Health Care	No		Recent publications demonstrate that during the acute phase of treatment of upper limb lymphoedema, a two layer compression system provides		Thank you for providing details of the study by Moffat et al., 2011. An assessment of the abstract did not determine if the study addressed lymphoedema management in patients with advanced

			better reduction in upper limb volume while being applied twice a week as compared to five times a week for standard bandaging. Both compression therapy regimens were accompanied by manual lymphatic drainage. This evidence allows a much increased availability of specialist physiotherapy services for breast cancer patients by greatly increasing patient capacity in lymphoedema clinics. Ref. Moffat CJ, Franks P et al A preliminary RCT to determine the application frequency of a new lymphoedema bandaging system. British J Dermatol. Accepted for publication, 2011.		breast cancer. This area will be examined again in the next review of the guideline.
3M Health Care	No		A recently published qualitative study has		Thank you for providing details of the study by

			demonstrated that changing to a two layer compression bandage treatment for lymphoedema patients improves their quality of life, by providing a lighter, quicker, allowing increased mobility, increased patient confidence, together with a sense of control and well being. Ref. Morgan, P. A., Murray, S., Moffatt, C. J. and Young, H. (2011) International Wound Journal. 8 (6) 586-598.		Morgan et al., 2011. However, through an assessment of the abstract it was not possible to determine if the study addressed lymphoedema management in patients with advanced breast cancer. This area will be examined again in the next review of the guideline.
3M Health Care	No		A recently published study demonstrates a significantly greater reduction in patient limb volume when utilising a two layer compression system as compared to traditional treatment with conventional inelastic multicomponent compression bandage systems. Ref.		Thank you for providing details of the study by Lamprou et al., 2011. However, through an assessment of the abstract it was not possible to determine if the study addressed lymphoedema management in patients with advanced breast cancer. This area will be examined again in the next review of the guideline.

			LAMPROU, D.-A., DAMSTRA, R. J. and PARTSCH, H. (2011), Prospective Randomized, Controlled Trial Comparing a New Two-Component Compression System with Inelastic Multicomponent Compression Bandages in the Treatment of Leg Lymphedema. Dermatologic Surgery, 37: 985–991.		
3M Health Care	No		The three pieces of recently published data (2011/2012) supporting the use of new compression therapy alternatives for lymphoedema patients has shown that patient outcomes are improved, patients can receive a relatively enabling therapy affording greater mobility and lymphoedema services can treat a greater number of patients with their		Thank you for providing studies relating to lymphoedema management. However, through an assessment of the abstracts it was not possible to determine if the studies addressed lymphoedema management in patients with advanced breast cancer. This area will be examined again in the next review of the guideline. It has been proposed that this will be carried out in one year as opposed to in three years time.

			limited resources. These three pieces of evidence were not available at the time the literature review was undertaken that under pins the recommendation not to undertake an update to the CG81 guideline, at this time. In view of the current availability of these three pieces of evidence it would be to the detriment of lymphoedema services and the attending patients if the update was delayed for a further 3 years.		
RCN		There are no objections to the proposals not to update the guideline at this time. It is noted that this decision 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. Also noted is the proposal to cross reference the guideline to new Technology Appraisals (TA214 and TA239) which were previously not mentioned.			Thank you for your comment.

Roche Products Limited	Yes	In light of the changing landscape of advanced breast cancer treatment, we support NICE's proposal to delay the review of this guideline for a further year. In addition to the technology appraisals mentioned (TA214 and TA239), further data will be available which was not identified in the systematic review that informed the consultation document, including data from the following clinical trials: • CLEOPATRA: A pivotal Phase III study investigating the efficacy and safety of the combination of pertuzumab, Herceptin and chemotherapy compared with Herceptin and chemotherapy alone in HER2-positive metastatic breast cancer (CLEOPATRA) • EMELIA: A Phase III Randomized, two arm multi-centre open label clinical trial comparing efficacy and safety of single agent T-DM1 vs. Capecitabine + Lapatinib in HER2 positive incurable locally advanced or metastatic BC • MARIANNE: A randomised, three-arm, multi-centre, Phase III study to evaluate the efficacy and safety of trastuzumab emtansine (T-DM1) as a first-line treatment in patients with HER2-positive metastatic breast cancer (MARIANNE)			Thank you for providing information about relevant ongoing trials. As the trials are currently ongoing we will examine these areas in the next review of the guideline.
Roche Products		We would also like to clarify the following			Thank you for your

Limited		On Page 9-10 of the review document the following statement reads: “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.” The above statement is inconsistent with the current Guideline, which states (P.48) “The GDG acknowledged that the existence of price discounts for paclitaxel can significantly alter the cost effectiveness of the sequences examined in the analysis’. The guideline therefore suggests that paclitaxel might, under some circumstances be used as an alternative to docetaxel.			comment. The current guideline recommendations are as follows: • For patients with advanced breast cancer who are not suitable for anthracyclines (because they are contraindicated or because of prior anthracycline treatment either in the adjuvant or metastatic setting), systemic chemotherapy should be offered in the following sequence: − first line: single-agent docetaxel − second line: single-agent vinorelbine or capecitabine − third line: single-agent capecitabine or vinorelbine (whichever was not used as secondline treatment). • 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. Through the review of the guideline, new literature was identified relating to paclitaxel. 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. This area will be examined again in the next review of the guideline.
Roche Products Limited		Additionally we would like to acknowledge that there are currently two studies ongoing with Pertuzumab and Herceptin which should be mentioned (P.40). The additional study is highlighted in red below.			Thank you for your comment.
Roche Products Limited		Pertuzumab and trastuzumab (Two studies)			Thank you for providing information about relevant

		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. Randomised, double-blind, placebo-controlled Phase III trial which evaluated efficacy and safety of the combination of pertuzumab plus trastuzumab plus docetaxel in advanced breast cancer. Median progression-free survival was extended by 6.1 months (12.4 months vs 18.5 months, HR 0.62, p<0.001) compared to trastuzumab plus docetaxel alone. Objective response rate was 80.2% in the pertuzumab group. There is no increase in cardiac toxic effects and is generally well tolerated. Whilst immature currently, interim analysis of overall survival (165 events) demonstrated a strong trend in favour of pertuzumab group. Final analysis of overall survival will be performed after 385 deaths have occurred.			ongoing trials. As the trials are currently ongoing we will examine these areas in the next review of the guideline.
Breast Cancer Campaign	Yes	Breast Cancer Campaign agrees that the guideline should be reviewed again in one year rather than in three years' time to ensure the timely consideration of upcoming Technology Appraisal outcomes.			Thank you for your comment.

Amgen Limited	Yes	We agree with the Centre for Clinical Practice recommendation that CG81 should be reviewed in one year to enable relevant Technology Appraisals (due to be published in 2012) to be taken into consideration. We wish to highlight the omission of a relevant Technology Appraisal in the review consultation document that is currently in progress (denosumab for the treatment of bone metastases from solid tumours, publication date: August 2012; available at: http://guidance.nice.org.uk/TA/Wave21/6). This Technology Appraisal will provide guidance related to bone metastases with respect to managing complications (review consultation document; clinical area 6).	None	None	Thank you for your comment. The related Technology Appraisal that you have highlighted has been added to the table in Appendix 1 and will be taken into consideration in the next review of the guideline as it is due to be published in 2012.
Breakthrough Breast Cancer		Since these guidelines were issued in 2009 a number of trials have been conducted on clinical areas relating to breast cancer. Based on the evidence presented in your review we are satisfied with your decision to review the guidelines next year when relevant Technology Appraisals (TAs) have been published and can be taken into consideration. It should also be noted that as well as the TAs you have cited there are two important technologies that have been proposed for appraisal which may need to be considered at a later date.		No comment	Thank you for your comments.

		The first is for pertuzumab in combination with trastuzumab and a taxane for the treatment of HER2 positive metastatic breast cancer. If a technology appraisal is undertaken for this drug (pertuzumab) it may have an impact on the guideline recommendations. Much of the data that informs this proposed appraisal comes from a study by Baselga *et al*. This study describes the CLEOPATRA trial where pertuzumab in combination with trastuzumab and docetaxel is compared with trastuzumab plus a docetaxel alone. Baselga J, Cortés J, Kim SB, Im SA, Hegg R, Im YH, Roman L, Pedrini JL, Pienkowski T, Knott A, Clark E, Benyunes MC, Ross G, Swain SM; CLEOPATRA Study Group. Pertuzumab plus trastuzumab plus docetaxel for metastatic breast cancer. The New England Journal of Medicine 2012 12;366(2):109-19 The appraisal for everolimus in combination with exemestane for the treatment of advanced or metastatic HER2 negative, oestrogen receptor positive breast cancer after prior endocrine therapy is also in development. If this technology appraisal is undertaken it may have an impact on the guideline recommendations. For more information on the data that informs this proposed technology appraisal please see Baselga *et al*. Baselga J, Campone M, Piccart M, Burris			Related published and in-progress Technology Appraisals will be examined in the next review of the guideline.

		HA 3rd, Rugo HS, Sahmoud T, Noguchi S, Gnant M, Pritchard KI, Lebrun F, Beck JT, Ito Y, Yardley D, Deleu I, Perez A, Bachelot T, Vittori L, Xu Z, Mukhopadhyay P, Lebwohl D, Hortobagyi GN. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. New England Journal of Medicine. 2012;366(6):520-9. For lymphoadema management it may be appropriate to consider guidelines from NCAT that state patients treated for breast cancer should be screened for the early onset of lymphoedena through assessment of the at risk limb both before and after surgery or radiotherapy. It may be beneficial to consider the evidence used for these guidelines. National Cancer Action Team. 2009. Rehabilitation Care Pathway: Lymphoedema Furthermore, we would like to stress that if other respondents to this review identify specific evidence that does or may in the future influence clinical practice for the diagnosis and treatment of advanced breast cancer then this should be considered. If this is the case it may be necessary to review the guidelines before 2013 as cited in the consultation document.			Early recognition of lymphoedema in patients with early, locally advanced or advanced breast cancer was assessed through a focused search. 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. This area will be examined again in the

					next review of the guideline.
GlaxoSmithKline	Yes	The recommendation by NICE that the guideline should not be considered for an update at this time but will be reviewed again in one year, is acceptable.	No comment	No comment	Thank you for your comment.
GlaxoSmithKline		The technology appraisal that is in progress for 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 has been included under the lapatinib studies on page 37, but omitted from the trastuzumab studies on page 38.			Thank you for your comment. All related NICE guidance can be found in Appendix 1 and will be taken into consideration in the next review of the guideline.
GlaxoSmithKline		On page 97, Reference 1, the name of the first author is incorrect. 'Di LA' should be replaced with 'Di Leo A'			Thank you for highlighting this inaccuracy, this has been noted.
GlaxoSmithKline		On page 111, Reference 127, the name of the first author is incorrect. 'Di LA' should be replaced with 'Di Leo A'			Thank you for highlighting this inaccuracy, this has been noted.
GlaxoSmithKline		On page 110, References 121 and 122, the name of the first author is incorrect. 'von MG' should be replaced with 'von Minckwitz G'.			Thank you for highlighting this inaccuracy, this has been noted.
Novartis	Yes	Novartis agrees that the guideline should not be updated now. It will be more appropriate to review and update the guideline in a year's time.	n/a	n/a	Thank you for your comment.
The Royal College	Yes	The RCR agrees that a full review is not			Thank you for your

of Radiologists		needed for CG81, but the review document with the summary of the evidence should be made available. We note that a full update in a year is recommended due to the large number of trials to evaluate. When a full update is performed we suggest it should also consider whether there are any additional questions to be answered by a clinical guideline. The RCR agrees that TA214/239 need to be referenced now.			comments.
The Royal College of Radiologists		With regard to combination versus sequential single agent chemotherapy the comments made by CG81 still stand. However, the RCR suggests that a specific statement should be made that "the combination of vinorelbine and capecitabine is an accepted regime". Clinicians would then have the choice of these two drugs as sequential single agents or combination therapy without adding additional drugs to the portfolio agreed by NICE. (We understand that not all departments are allowed to give the combination using the CG81 wording, hence the need for clarification).			Thank you for your comment. Through the review of the guideline one study was identified which evaluated the efficacy and safety of sequential versus simultaneous use of vinorelbine and capecitabine for metastatic breast cancer. However, as only a single trial was identified it would be premature to update the guideline at this time. This area will be examined again in the next review of the guideline.
The Royal College of Radiologists		We suggest that use of the tumour markers CA15.3 and CEA can wait for an update. Similarly we suggest that lymphoedema will warrant a full assessment on the update.			Thank you for your comment. These areas will be examined again in the next review of the guideline.

Celgene UK Ltd	No.	Celgene welcomes the opportunity to comment on this guideline review proposal. As the current manufacturer of nab-paclitaxel (Abraxane™) Celgene is concerned that Clinical Guideline 81 (Advanced Breast Cancer Diagnosis and treatment, issued in 2009) does not include any reference to - or make any recommendations in relation to – the use of nab-paclitaxel in the treatment of advanced breast cancer. Specifically, the pivotal Phase III study of nab-paclitaxel in advanced breast cancer (Gradishar et al, J Clin Oncol, 2005 – copy attached) was omitted from the previous review and should be included.	None.	None.	Thank you for your comment. Nab-paclitaxel was omitted from CG81 as the drug was not licensed until near the end of the guideline development. Through the review of CG81 four studies were identified relating to nab-paclitaxel: • An RCT comparing nab-paclitaxel with solvent-based paclitaxel (sb-paclitaxel) in patients with metastatic breast cancer • An RCT comparing weekly nab-paclitaxel with docetaxel • Two economic analyses of albumin-bound paclitaxel As the studies identified compare nab-paclitaxel with different comparators, it would be premature to consider updating the guideline at this time. This area will be examined again in the future review of the guideline.
Celgene UK Ltd	No.	The pivotal phase III study for nab-paclitaxel (Gradishar 2005), was published			Thank you for your comment. The review of

		in JCO and demonstrates that metastatic breast cancer patients who have failed first-line treatment for metastatic disease and for whom standard anthracycline containing therapy is not indicated, have an overall survival benefit of 2.3 months. This trial was not included in the evidence used to develop CG81. The updated literature search performed by the National Collaborating Centre has only reviewed the updated evidence for advanced breast cancer from literature published between 2009 and 2012 (i.e. since the date of publication of CG81). While this is understandable, it does mean that the updated review does not include the 2005 pivotal phase III study. As a minimum, therefore, Celgene requests that this important publication be included in the latest evidence review and taken into consideration when deciding whether or not there is sufficient new evidence to warrant an early update of CG81.			CG81 was conducted by NICE with the aim of considering new evidence published since the publication of the guideline (date period 2008-2012). The purpose of the review is to attempt to identify where there is a significant amount of new evidence that might warrant an update of the guideline recommendations. As such, the reference you supplied is outwith our date period of review. Through the review of CG81 four studies were identified relating to nab-paclitaxel: • An RCT comparing nab-paclitaxel with solvent-based paclitaxel (sb-paclitaxel) in patients with metastatic breast cancer • An RCT comparing weekly nab-paclitaxel with docetaxel • Two economic analyses of albumin-bound paclitaxel As the studies identified

					compared nab-paclitaxel with different comparators, it would be premature to consider updating the guideline at this time. This area will be examined again in the future review of the guideline.
Celgene UK Ltd	No.	The review group has stated that the use of paclitaxel as a monotherapy is not included in the existing CG81 guideline recommendations due to heterogeneity among the studies found and recommends further research. Celgene is not convinced that this is a valid enough reason to exclude new innovations harnessing the clinical efficacy of paclitaxel which could benefit patients. Celgene had conducted an indirect comparison of nab-paclitaxel with docetaxel (to support its submissions to both the SMC and AWMSG), the results of which indicated non-inferiority of efficacy and believes that it maybe possible for NICE to undertake an independent assessment. Celgene is pleased to note that the review group has referenced two phase 2 monotherapy studies for nab-paclitaxel: Dranitsaris G et al (2010) and Gradishar (2009). However, this makes it			Thank you for your comment. Through the review of CG81, three studies were identified related to paclitaxel for advanced breast cancer. However, we considered the new literature too heterogeneous, including comparisons of different treatment regimens, to make a conclusion about the efficacy of paclitaxel as a monotherapy for advanced breast cancer at this time. This area will be examined again in the next review of the guideline. Thank you for your comment however the 2005 Gradishar study is outwith our date period of review.

		all the more important that the 2005 pivotal phase 3 trial is also included in the review of the available evidence base. By limiting references mostly to sb-paclitaxel in the consultation document the review group inadvertently is excluding patients and treatment pathway positions where nab-paclitaxel could have a potential benefit. Celgene therefore requests that the group consider the merits of nab-paclitaxel as a monotherapy and not limit its review to looking at nab-paclitaxel in the same light as sb-paclitaxel.			Thank you for your comment. All references identified through the review process relating to sb-paclitaxel and nab-paclitaxel which met the inclusion criteria (as defined in CG81) were included in the consultation document. The review process involves an assessment of abstracts, as opposed to a full systematic review of the guideline. As such, it was not possible to confirm whether the identified studies which included paclitaxel as an intervention evaluated the sb-paclitaxel or nab-paclitaxel formulations.
Celgene UK Ltd	No.	Irrespective of the published literature, there are a number of reasons why it is important that national guidance on the use of nab-paclitaxel should be issued to the NHS in England and Wales as soon as practicable. The provisional decision not to update CG81 in 2012 would therefore be extremely disappointing for the following			Thank you for your comment. Through the review of CG81 four studies were identified relating to nab-paclitaxel:

		reasons: • Nab-paclitaxel is licensed in the UK and elsewhere for the "monotherapy treatment of metastatic breast cancer in adult patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated". Abraxane® is used in the NHS in this clinical setting. • Nab-paclitaxel (Abraxane) is already accepted for restricted use within NHS Scotland following a review by the Scottish Medicines Consortium (SMC). The SMC concluded that nab-paclitaxel was cost-effective within its label for patients who would otherwise have received docetaxel or sb-paclitaxel for second line treatment. Use in NHS Scotland is restricted to patients who would otherwise receive docetaxel or 3-weekly solvent-based paclitaxel as second-line treatment for metastatic breast cancer. • Nab-paclitaxel (Abraxane) is also recommended as an option for use within NHS Wales for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated.			• An RCT comparing nab-paclitaxel with solvent-based paclitaxel (sb-paclitaxel) in patients with metastatic breast cancer • An RCT comparing weekly nab-paclitaxel with docetaxel • Two economic analyses of albumin-bound paclitaxel As the studies identified compared nab-paclitaxel with different comparators, it would be premature to update the guideline at this time. This area will be examined again in the future review of the guideline.

		• A number of Strategic Health Authorities in England have accepted nab-paclitaxel (Abraxane) for funding under the Cancer Drug Fund. Celgene is therefore of the view that any review decision on CG81 should be based, not only on the available published evidence, but should also take into account current clinical practice and the absence of a national guidance on nab-paclitaxel in the NHS in England.			
Celgene UK Ltd	No.	Significant evidence in the management of metastatic breast cancer has been presented in 2011 which will result in a paradigm shift, including BOLERO-2 (Everolimus) and CLEOPATRA in HER2+ breast cancer, SABCS 2011 (combination of Pertuzumab and Trastuzumab). In the light of new clinical evidence, it is important that these new regimes are examined as these are likely to be a part of the future standards of care.			Thank you for providing information about relevant ongoing trials. As the CLEOPATRA trial is currently ongoing (final data collection date for primary outcome measure is expected in 2012) and the BOLERO-2 trial final data collection date for the primary outcome measure is expected in 2013 we will examine these areas again in the next review of the guideline.
The Society and College of Radiographers		The review confirms that there are no areas where a significant change in clinical practice is required.			Thank you for your comment.
Breast Cancer Care	Agree with decision but	We agree with the decision based on new evidence but are aware of some areas of			Thank you for your comment. We have

	suggest review in one year will be necessary	discordance between practice and the guidelines – arising from disagreement with some of the guidance among key clinicians.			proposed that the guideline be reviewed in one year rather than in three years time.