National Institute for Health and Clinical Excellence

BREAST CANCER (ADVANCED)
Guideline Consultation Comments Table
13 AUGUST – 08 OCTOBER 2008

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
SH	3 Counties Cancer Network Palliative Care Lead Clinicians Group	1				This organisation was approached but did not respond.	
SH	Abbott Laboratories Limited	2				This organisation was approached but did not respond.	
SH	Abbott Molecular	3.0	General			**If you have any comments about these two definitions of HER2 positive status, for the two breast cancer populations** New UK guidelines for Her-2 testing have been published in April 2008. These supercede references to testing made in earlier guidelines (TA34) Her-2 testing in the UK-Further update to Recommendations. Walker et. Al. J. Clin. Pathol. 1st April 2008. UK Her-2 testing guidelines recommend Front line testing using FISH (fluorescent ISH) OR IHC with confirmation of 2+ cases using an ISH techniques UK Her-2 testing guidelines recommend that not less than 200 IHC tests should be carried out to obtain good quality, however only 100 FISH tests. Therefore labs perfoming between 100 and 250 her-2 tests should either send out all cases or do front	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines. TA34 was published in 2002, and we acknowledge that the guidelines for HER2 testing have changed since that time. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	Abbott Molecular	3.1	Full	32	45	In Pathology section there is no comment on pathology testing protocol for Her-2 status, but accuracy of this testing strategy has a profound clinical and economic effect.	This level of detail would not be appropriate to include in the background information
SH	Abraxis Oncology	4				This organisation was approached but did not respond.	

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SH	Afiya Trust, The	5				This organisation was approached but did not respond.	
SH	Age Concern Cymru	6				This organisation was approached but did not respond.	
SH	Age Concern England	7				This organisation was approached but did not respond.	
SH	Airedale Acute Trust	8.0	Full guidance ABC	31	45	The first recommendation says,"PET-CT should only be used…….". However there may be situations where PET might be helpful in addition to the recommendation above, for example prior to resection of metastases to exclude other metastases not apparent on CT, therefore to say "only" might be very restrictive	In situations such as these, local protocols should be followed, and we do not feel that we need to be explicit in the guideline. Guidelines are intended to cover the majority of clinical situations, not all possible situations.
SH	Airedale Acute Trust	8.1	Full guidance ABC	60	21-23	Recommendation 5 says,"Patients who are receiving treatment with trastuzumab should not continue trastuzumab at the time of disease progression outside the central nervous system". This is contrary to recent evidence presented at ASCO where the recommendation is to continue herceptin beyond progression. I appreciate the guideline only covered the evidence till 30.6.8, but ASCO evidence was presented a month before this date. I appreciate there are cost implications to this.	Trastuzumab is not currently licensed for this indication. It would be difficult to make such a recommendation without good cost-effectiveness data.
SH	Airedale Acute Trust	8.10	Full guidance ABC	52 General comment	18-25 ----------	Another important question which has not been addressed is that how long should capecitabine and vinorelbine be continued for? Some oncologists continue these agents indefinitely as long as patients respond and / or till unacceptable toxicity, but some discontinue after 6 months. I feel this area creates variation in practise, reducing which was the prime aim of this guideline	We felt that there was insufficient evidence on which to base recommendations about duration of chemotherapy.
SH	Airedale Acute Trust	8.11	Full guidance ABC	60 General comment	21-23 ----------	Lapatinib has been mentioned in passing but no indication as to whether this is going to be reviewed?	Lapatinib is the subject of a technology appraisal and therefore has not been covered in this guideline. We have discussed this in the background to the recommendation on p59.

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						As herceptin beyond progression is not recommended, neither is lapatinib, so that means these patients who progress should get neither?	We recognise the clinical dilemma but trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data. Lapatinib is the subject of a technology appraisal and therefore has not been covered in this guideline.
SH	Airedale Acute Trust	8.2	Full guidance ABC	31	45	Same comment as comment no 1 re PET-CT	In situations such as these, local protocols should be followed, and we do not feel that we need to be explicit in the guideline. Guidelines are intended to cover the majority of clinical situations, not all possible situations.
SH	Airedale Acute Trust	8.3	Full guidance ABC	32	44	It might be helpful to add in another bullet point regarding patients who need biopsy, to include those who present with metastatic disease 5 or more years after diagnosis of primary early breast cancer	We disagree. The bullet points are examples only, they are not meant as an exhaustive list. Also in many clinical situations where multiple metastases are present, a long disease free interval would not be considered an indication for re-biopsy.
SH	Airedale Acute Trust	8.4	Full guidance ABC	60	21	Same comment as comment no 2 regarding herceptin continuation	Trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data.
SH	Airedale Acute Trust	8.5	Full guidance ABC	72	12	Where it reads, "dated RCTs", is that a typo? Does it mean outdated RCTs?	The use of the word 'outdated' was intended to indicate age rather than possible irrelevance. The word has been changed to 'old' for clarity.
SH	Airedale Acute Trust	8.6	Full guidance ABC	85	17	Says "both intrathecal and intravenous chemotherapy improved patient survival", but no recommendation has been made either for or against intrathecal chemotherapy, also which particular one to use? I appreciate data in this area is sparse. Is this something NICE are planning to review?	The wording of the evidence summary has been revised. The GDG did not feel there was sufficient evidence on which to base a recommendation on intrathecal chemotherapy.
SH	Airedale Acute Trust	8.7	Full guidance ABC	98	4	Comments, "toxic deaths can only occur after first cycle", however it is common experience to see bad toxicity / toxic deaths with capecitabine after second cycle	Due to the multitude of treatment options considered in the economic model, we had to keep the model structure simple. The structure we used was adapted from Leung et al and the assumptions were validated by the GDG. We acknowledge that toxic deaths can occur at different points in the treatment course, however since these are very

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							rare events this simplification is unlikely to have a big impact on the results of the model.
SH	Airedale Acute Trust	8.8	Full guidance ABC	124	2	Chemotherapy is defined as "a chemical that specifically binds to and kills tumour cells", however this is not true, chemotherapy does not specifically kill cancer cells, it kills cancer and normal cells, hence the toxicity	We will amend the text.
SH	Airedale Acute Trust	8.9	Full guidance ABC	General comment	--------	The guideline has not looked at role of tumour markers in follow up / treatment monitoring	The scope of this guideline (diagnosis and treatment of patients with advanced breast cancer) was very broad and it was not possible for the GDG to cover all of the topics within the limited development time. They therefore had to prioritise which topics the guideline would focus on and the role of tumour markers in follow-up/treatment monitoring was not considered a priority for investigation.
SH	Almac Diagnostics	9				This organisation was approached but did not respond.	
SH	Anglesey Local Health Board	10				This organisation was approached but did not respond.	
SH	Arden Cancer Network	11				This organisation was approached but did not respond.	
SH	Association of Breast Surgery at BASO	12.0	Full	44	44	The best publication which looked at this: chemotherapy with subsequent endocrine therapy versus chemotherapy alone or hormone therapy alone in ER positive disaese showed no advantage in response rates or in survival. Indeed the survival of AC & Tam was numerically less than endocrine therapy (or chemotherapy) alone - Australian & New Zealand Breast Cancer Group. (J Clin Oncol. 1986 4;186-193). This study also reported that the response rates to endocrine therapy post chemotherapy (AC) were much lower 5.5% than vice versa (34.7%). This study therefore supports section 1.3.1.1 in recommending endocrine therapy unless there is imminent life-threatening disease.	Thank you for this observation. We agree.
SH	Association of Breast Surgery at BASO	12.1	Full	21	2	The figure describingendocrine treatment pathways states that chemotherapy should be given when a	These algorithms are intended to be a pictorial overview of the recommendations in the guideline

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						rapid response is needed. The figure should perhaps make clear that 'rapid response' is usually only required if there is immenent life-threatening visceral disease – what the NCCN guidelines describe as a 'visceral crisis'.	not a substitute for them. Since both algorithms and recommendations are intended to be read together, some detail has been removed from the algorithms to make them easier to understand.
SH	Association of Breast Surgery at BASO	12.2	Full	47	9	Ovarian ablation is the earliest endocrine therapy and should still be considered for first-line treatment. Indeed there is evidence that the combination of ovarian ablation plus tamoxifen should be considered if one wants to maximise the chance of response. For example where the physician is concerned that the patient may only have one potential chance of endocrine therapy (eg a young woman with ER positive visceral discease). The guidelines should not be prescriptive about what endocrine agent(s) to use since if a patient with an ER positive tumour responds to endocrine therapy it is not only the benefit of that agent which is important but the fact that this opens up a whole class of drugs which she might equally benefit from and delay the use of chemotherapy. We would suggest suggest that the recommendations 1.3.1.2 & 1.3.1.3 of the guidelines be combinaed to simply state that "In pre-menospausal women ovarian ablation and tamoxifen, alone or in combination should be considered as first and second line endocrine therapy." The guidelines make no mention of the newer endocrine agent, fulvestrant, which has also been shown in 3 large, randomised clinical trials to be efffective after tamoxifen and also after third generation aromatase inhibitors. This agent provides another treatment option for patients with hormone responsive advanced breast cancer and for some patients will delay the need for chemotherapy which is both ethically appropriate as well as cost-effective. The guidelines should state that fulvestrant is another endocrine therapy option which should be considered	There is one randomised trial comparing buserelin in combination with Tamoxifen with either agent alone. This is a relatively small study, and no confirmatory trial has been performed. However on review of this evidence the GDG felt that the recommendation should be changed as suggested. The evidence appraised for this topic did not show an advantage for fulvestrant over aromatase inhibitors as a treatment for postmenopausal women. The GDG did not feel able to recommend the use of fulvestrant on the basis of this evidence.

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						for hormone responsive advanced breast cancer.	
SH	Association of Breast Surgery at BASO	12.3	Full	80	44	The randomised trials of bisphosponates were not limited to patients with newly diagnosed ER positive bone metastases. Indeed the studies entered patients who had received a number of prior therapies and therefore were significantly down the treatment pathway. Sixty to seventy percent of ER positive tumours respond to first line endocrine therapy with an average duration of response of 12-18 months, and in many patients the duration of response is much longer. In patients responding to endocrine therapy bisphosphonates are unlikely to add to the prevention of skeletal related events since the endocrine therapy is controlling the disease. This in addition to a lack of evidence for bisphosphonates with first line endocrine therapy should perhaps make the statement less definite. There is also significant cost (in terms of potential side-effects) associated with what may be a very marginal benefit at this stage of their disease. We would suggest "consider' rather than 'offer' would be more appropriate.	We have changed the text to "consider".
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	13.0	FULL	General		The whole issue of rehabilitation for these patients is rather glossed over and could have more emphasis placed on it.	The issue of rehabilitation is an important one, unfortunately there is limited high-quality evidence available on this. We feel that we have drawn attention to rehabilitation issues as much as we are able to given the limited evidence.
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	13.1	FULL	71	All	The issue of pain management, a significant issue for patients with bony disease, could be dealt with in a little more detail. It is generally accepted cancer related pain needs a multi dimensional holistic approach with use of drug and non-drug approaches. Useful new resource – "breaking barriers" management of cancer related pain: educational CD ROM developed by Cancer research UK and the Royal Marsden 2008. It may be helpful to mention some of the non-drug	The issue of pain management goes beyond patients with advanced breast cancer. It was not identified as a priority topic for the GDG to investigate in this guideline.

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						approaches that have been well researched in non cancer pain – pacing of activity etc. Also Cochrane review on TENS which identified need for further research and was not able to establish effectiveness.	
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	13.2	FULL	75	All	Can there be clarification of whether CBD is different to MLD? And there is no mention of SLD – where does this fit in? Would it be appropriate to recommend giving patients written information on lymphoedema?	We are not familiar with the term CBD so we are not able to answer this query. SLD is included in the "simpler maintenance treatments" mentioned on p77, line10 We have included provision of written information in the recommendations
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	13.3	FULL	77	34	There could be more detail on the role of exercise in cancer related fatigue as this is one of the best researched areas and could be more detailed.	We do not think this level of detail is appropriate for the background information. More information on the evidence for exercise in cancer related fatigue can be found in the evidence review which accompanies this guideline.
SH	Association of Chartered Physiotherapists in Oncology and Palliative Care	13.4	FULL	109	9	Package 1 must have some therapy funding included as patients with advanced disease and associated problems such as lymphoedema and bone secondaries, might still be receiving chemotherapy and will need some form of rehabilitation. It is not sufficient to have this in package 2 alone.	The packages are artificial constructs designed for use in the model. There is no assumption that each individual will receive precisely this pattern of care, rather this was an attempt to estimate the costs of supportive care in general at this point in the patient pathway.
SH	Association of Surgeons of Great Britain and Ireland	14				This organisation was approached but did not respond.	
SH	Association of the British Pharmaceuticals Industry (ABPI)	15				This organisation was approached but did not respond.	
SH	AstraZeneca UK Ltd	16.0	Full	General		AstraZeneca welcomes the opportunity to comment on the draft Advanced Breast cancer Clinical Guidelines. AstraZeneca is pleased that fulvestrant has been recognised in the evidence considered for these guidelines and are pleased that anastrozole has been recognised in as a treatment option in advanced	Thank you

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						breast cancer. AstraZeneca agrees that patient choice is paramount in treatment decision-making especially when the disease is in its advanced stage. Women should be fully informed of the advantages and disadvantages of medical and surgical treatment, understanding the overall benefits of treatment and the impact treatment has on quality of life	
SH	AstraZeneca UK Ltd	16.1	Full	46-48	20-5	With respect to the section 4.1 of the full guidelines AstraZeneca feels that use of fulvestrant in patients failing previous anti-oestrogen therapy has been omitted. The evidence reviewed in this section seems to have overlooked two RCTs and two pooled analyses where fulvestrant showed non-inferior efficacy to anastrozole. AstraZeneca suggests on the strength of this evidence, fulvestrant should be suggested as an option in this patient group as it increases the choice available to both clinicians and patients. **References:** 1. Howell A, Robertson J, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg U, Vergote I, Erikstein B, Webster A, and Morris C (2002) Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment, Journal of Clinical Oncology, 20(16): 3396-3403 2. Anthony Howell, John Pippen, Richard M. Elledge, Louis Mauriac, Ignace Vergote, Stephen E. Jones, Steven E. Come, C. Kent Osborne, John F. R. Robertson (2005) Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma: A Prospectively Planned Combined Survival Analysis of Two Multicenter Trials. CANCER July 15, 2005 / Volume 104 / Number 2. Page 236-239. 3. Robertson J, Osborne CK, Howell A, Jones S,	The evidence appraised for this topic did not show an advantage for fulvestrant over aromatase inhibitors as a treatment for postmenopausal women. The GDG did not feel it was necessary to recommend the use of fulvestrant on this basis.

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						Mauriac L, Ellis M, Kleeberg U, Come S, Vergote I, Gertler S, Buzdar A, Webster A, Morris C (2003) Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma in Postmenopausal Women: A Prospective Combined Analysis of Two Multicenter Trials, CANCER, 98(2): 229-238 4. Osborne CK, Pippen J, Jones S, Parker L, Ellis M, Come S, Gertler S, May J, Burton G, Dimery I, Webster A, Morris C, Elledge R, and Buzdar A (2002) Double-Blind, Randomized Trial Comparing the Efficacy and Tolerability of Fulvestrant Versus Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing on Prior Endocrine Therapy: Results of a North American Trial, Journal of Clinical Oncology, 20(16): 3386-3395	
SH	AstraZeneca UK Ltd	16.2	NICE (1.3.2)	46-47	38-20	With respect to the section 1.3.2 in the NICE version AstraZeneca feels that the use of fulvestrant in patients failing previous anti-oestrogen therapy (see previous comment regarding section 4.1 of the full guidelines) has been omitted. AstraZeneca suggests that this information should be reflected across to the NICE guideline. **References** 1.Howell A, Robertson J, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg U, Vergote I, Erikstein B, Webster A, and Morris C (2002) Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment, Journal of Clinical Oncology, 20(16): 3396-3403 2.Anthony Howell, John Pippen, Richard M. Elledge, Louis Mauriac, Ignace Vergote, Stephen E. Jones, Steven E. Come, C. Kent Osborne, John F. R. Robertson (2005) Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma: A Prospectively Planned Combined Survival Analysis of Two Multicenter Trials. CANCER July 15, 2005 /	The evidence appraised for this topic did not show an advantage for fulvestrant over aromatase inhibitors as a treatment for postmenopausal women. The GDG did not feel able to recommend the use of fulvestrant on the basis of this evidence.

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						Volume 104 / Number 2. Page 236-239. 3.Robertson J, Osborne CK, Howell A, Jones S, Mauriac L, Ellis M, Kleeberg U, Come S, Vergote I, Gertler S, Buzdar A, Webster A, Morris C (2003) Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma in Postmenopausal Women: A Prospective Combined Analysis of Two Multicenter Trials, CANCER, 98(2): 229-238 4.Osborne CK, Pippen J, Jones S, Parker L, Ellis M, Come S, Gertler S, May J, Burton G, Dimery I, Webster A, Morris C, Elledge R, and Buzdar A (2002) Double-Blind, Randomized Trial Comparing the Efficacy and Tolerability of Fulvestrant Versus Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing on Prior Endocrine Therapy: Results of a North American Trial, Journal of Clinical Oncology, 20(16): 3386-3395	
SH	AstraZeneca UK Ltd	16.3	Appendices (Evidence Review)	98		In section 4.2.1 of the Evidence Review it is stated that 'The evidence base for this question comprises one guideline (Eisen et al, 2004), four systematic reviews (Mauriac et al., 2006; Gibson et al., 2007, Ferretti et al, 2006 and Crump et al,1997), three RCTs (Chia et al. 2008, Mouridsen et al,2007 and Goss et al, 2007) and a small, low quality comparative study (Catania et al,2007a).' The evidence base for this section seems to have omitted two additional RCTs and three pooled analyses for fulvestrant showing it to be as least as effective as anastrozole and that fulvestrant has clinical benefit when used in different lines of ABC therapy. Steger et al 2005 looks at fulvestrant in patients with ABC who have already received a wide variety of endocrine agents and chemotherapies, and are not eligible for inclusion in clinical trials. This paper demonstrates the ABC patients' 'real life experience' of fulvestrant. Given the lack of options in ABC either after tamoxifen or AI, AstraZeneca is	Data from references (1) (3) and (4) were presented by Mauriac *et al.* (2003) a study which was included in Gibson's 2007 Cochrane Review. The papers were not, therefore, individually appraised but the data they contained has been considered. Studies (2) and (5) have been appraised and will be included in the evidence review for this guideline.

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						disappointed that these studies have not been reviewed and suggests that they are incorporated within the final published full guideline. References 1. Howell A, Robertson J, Quaresma Albano J, Aschermannova A, Mauriac L, Kleeberg U, Vergote I, Erikstein B, Webster A, and Morris C (2002) Fulvestrant, Formerly ICI 182,780, Is as Effective as Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing After Prior Endocrine Treatment, Journal of Clinical Oncology, 20(16): 3396-3403 2. Anthony Howell, John Pippen, Richard M. Elledge, Louis Mauriac, Ignace Vergote, Stephen E. Jones, Steven E. Come, C. Kent Osborne, John F. R. Robertson (2005) Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma: A Prospectively Planned Combined Survival Analysis of Two Multicenter Trials. CANCER July 15, 2005 / Volume 104 / Number 2. Page 236-239. 3. Robertson J, Osborne CK, Howell A, Jones S, Mauriac L, Ellis M, Kleeberg U, Come S, Vergote I, Gertler S, Buzdar A, Webster A, Morris C (2003) Fulvestrant versus Anastrozole for the Treatment of Advanced Breast Carcinoma in Postmenopausal Women: A Prospective Combined Analysis of Two Multicenter Trials, CANCER, 98(2): 229-238 4. Osborne CK, Pippen J, Jones S, Parker L, Ellis M, Come S, Gertler S, May J, Burton G, Dimery I, Webster A, Morris C, Elledge R, and Buzdar A (2002) Double-Blind, Randomized Trial Comparing the Efficacy and Tolerability of Fulvestrant Versus Anastrozole in Postmenopausal Women With Advanced Breast Cancer Progressing on Prior Endocrine Therapy: Results of a North American Trial, Journal of Clinical Oncology, 20(16): 3386-3395 5. Steger G, Gips M, Simon S, Lluch A, Vinholes J, Kaufman B, Wardley A, Mauriac L. Fulvestrant ('Faslodex'): Clinical experience from the	

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						Compassionate Use Programme, CANCER TREATMENT REVIEWS (2005) 31, S10-S16	
SH	Bard Limited	17				This organisation was approached but did not respond.	
SH	Barnsley Hospital NHS Foundation Trust	18				This organisation was approached but did not respond.	
SH	Barnsley PCT	19				This organisation was approached but did not respond.	
SH	Bath and North East Somerset PCT	20				This organisation was approached but did not respond.	
SH	Baxter Healthcare Ltd	21				This organisation was approached but did not respond.	
SH	Bayer Healthcare PLC	22				This organisation was approached but did not respond.	
SH	Birmingham cancer network	23				This organisation was approached but did not respond.	
SH	Birmingham Clinical Trials Unit	24				This organisation was approached but did not respond.	
SH	Black Health Agency	25				This organisation was approached but did not respond.	
SH	Blaenau Gwent Local Health Board	26				This organisation was approached but did not respond.	
SH	Boehringer Ingelheim Ltd	27				This organisation was approached but did not respond.	
SH	Bournemouth and Poole PCT	28				This organisation was approached but did not respond.	
SH	Bradford & Airedale PCT	29				This organisation was approached but did not respond.	

SH	Breakthrough Breast Cancer & Breast Cancer Care	30.0				**If you have any comments about these two definitions of HER2 positive status, for the two breast cancer populations, please comment** It is our view that consistency between the early and locally advanced guideline and the advanced guideline is an important issue, as this will aid clarity and understanding and facilitate implementation. To this end, it is important that the definition of HER2 positive status is consistent across both guidelines. Given that the definition used in the early and locally advanced guideline is based on more recent evidence and recommendations in this field, for example UK testing recommendations, it may be helpful to consider applying this definition across both guidelines. As TA 34 is due to be updated shortly, similar modifications could be made to the definition used in that context in order to ensure wider consistency.	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines.TA34 was published in 2002, and we acknowledge that the guidelines for HER2 testing have changed since that time. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.1	Full	General		We welcome the opportunity to respond to the draft clinical guideline on *Advanced breast cancer: diagnosis and treatment*. This joint response from Breast Cancer Care and Breakthrough Breast Cancer is informed by our collective experience as leading breast cancer charities and the significant contact we have with people affected by advanced breast cancer across all areas of our work including research, service and information provision and policy and campaigning. In preparing this response we have drawn on the views and experiences of people affected by advanced and secondary breast cancer. The work we have undertaken under the umbrella of the Breast Cancer Care Taskforce on Secondary Breast Cancer in particular has provided significant insight into the views and experiences of people affected by secondary breast cancer (Breakthrough Breast Cancer is an active member of the Task Force).	Thank you

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						Breast Cancer Care's Secondary Breast Cancer Taskforce was established in 2006 to improve the treatment, support and care of secondary breast cancer patients. The Taskforce consists of a range of health professionals, people with secondary breast cancer, representatives from breast cancer charities and government health departments. The Taskforce is guided by people living with secondary breast cancer through membership of a User Advisory Group and of a wider Reference Panel. This submission also draws on the views and experiences of Breakthrough Breast Cancer's Campaigns & Advocacy Network (Breakthrough CAN) which brings together over 1100 individuals, regional groups and national organisations to campaign for improvements in breast cancer research, treatment and services. Our joint response to this consultation is further informed by a national survey of people affected by breast cancer (early and advanced) undertaken by Breast Cancer Care and Breakthrough Breast Cancer during August and September 2008. The survey asked a series of specific questions relevant to the draft guideline and was completed by over 200 respondents. Key themes and issues raised by respondents are highlighted throughout this response, together with a number of quotes and statistics. Overall, we welcome the draft guideline on advanced breast cancer and support the key recommendations that are set out in it. We particularly welcome the strong patient focus evident throughout; for example, through the inclusion of sections on provision of information and support for decision-making. We also welcome the recommendation for the appointment of a key worker for each individual patient with	Thank you.

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						advanced breast cancer, although feel the recommendation could be a stronger (as discussed in the relevant section of this response). However, while we support much of what is set out in the guideline we also have some concerns about omissions and areas that may not have been addressed in sufficient depth. These are set out below in the following general comment and throughout this response in relation to specific aspects of the Guideline.	We will respond to your specific queries below.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.10	Full	33	46	Breast Cancer Care and Breakthrough Breast Cancer believe there may be a potential argument for reconsidering the recommendation that patients with known oestrogen receptor status should not have a further biopsy upon secondary diagnosis. The clinical evidence cited by the draft guideline shows that approximately 15% of patients experience a change in receptor status (positive to negative). There is therefore a potential risk that a number of patients who are diagnosed with advanced breast cancer may receive treatment that is no longer appropriate to their individual case. Patients with advanced breast cancer tell us that quality of life is of great importance in the management of their condition and, consequently, it is important that patients are not exposed to potential side effects of treatments unnecessarily.	The evidence in this area is observational and of variable quality. The GDG did not feel that it warranted a recommendation, which would be a substantial change to current practice. These issues have been identified in the qualifying statement that accompanies this recommendation in the full version.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.11	Full	34	7	The feedback that we receive from people living with a diagnosis of advanced breast cancer suggests that there are wide variations in local practice in monitoring disease progression. We hope that the final guideline will go some way to ensure more consistent practice. However, we also feel that there is a need to emphasise the importance of providing patients will clear explanations about how the progression of the disease will be monitored, including information about	We hope so too. The GDG did not feel that it was possible to make recommendations on what imaging modalities should be used to monitor disease progress, or with what frequency because there would be wide

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						what to expect in relation to frequency of scans when symptoms require investigation. Many patients with advanced cancer expect active monitoring of their disease and can become anxious if there are not receiving regular interventions; for example, regular scans, thus clearer information may help to allay some of this anxiety. Nearly 30% of those who responded to our survey reported that they were not told about what imaging technique would be used to monitor the progression of their disease. Of those who were given an explanation, 70% said they found the information useful.	variation in imaging requirements depending on the clinical circumstances. The recommendations that were made were intended to avoid inappropriate routine use of these two modalities.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.12	Full	40	15	Respondents to our survey were asked which decision aids that they felt the final guideline should recommend. 85% said face-to-face counselling, 72% said question prompt sheets, 67% said meeting others in a similar situation, 35% said tape recordings of consultations and 29% said interactive computer programmes. This feedback highlights the wide range of preferences that different patients may have but also underlines the importance of the support provided by individuals – other people in a similar position or people with a counselling role. Breast Cancer Care and Breakthrough Breast Cancer feel that the draft guideline could be strengthened by highlighting the wealth of high quality information and support produced by organisations both within and outside the NHS that is available to health professionals. Many organisations, including Breast Cancer Care and Breakthrough Breast Cancer, produce information for patients and carers and work closely with the Department of Health and the NHS on piloting methods of facilitating improved access to this information for patients and healthcare professionals. These organisations also provide a range of other supportive interventions and aids for	Thank you for this information. We are not able to cite specific services in the full guideline. However in the patient version of the guideline that will be produced there is a section where organisations providing information and support can be listed.

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						example, through help-lines. Enabling access to these kinds of organisations and services can help to meet the information and support needs of patients.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.13	Full	41	5	People living with advanced breast cancer frequently tell us that assessments of their information and support needs may not always be effectively conducted or shared by all members of the oncology team. This is often because patients report they do not have access to a nurse specialist with skills and knowledge in managing advanced breast cancer. Efforts to respond to patient needs for information and involvement in decision-making can only be effective if they inform how the whole team works rather than some individual members. Our survey also found that 63% of respondents did not have their individual preferences for level and type of information assessed at all. Whilst we therefore welcome the recommendation that that individual needs should be assessed, this could potentially be strengthened to address the difficulty we have identified above in relation to information needs assessment. This recommendation could be extended to state that: "…The outcome of the assessment should be made available to all members of the multi-disciplinary team." It is our view that the appointment of a key worker, to take on a co-ordinating role similar to that of the breast care nurse for primary breast cancer patients, for every patient diagnosed with advanced breast cancer could improve the experience of patients in relation to effective communication, coordination and involvement in decision-making. The work of Breast Cancer Care's Secondary Breast Cancer Taskforce has shown that a key worker for advanced breast	Thank you for your observations. We are not recommending a formal, structured assessment as there is no evidence on which to base such a recommendation. Healthcare professionals should always make an assessment of an individual's information preferences. We agree that effective communication between members of the MDT is important at all times, but do not feel it necessary to make an explicit recommendation about this specific point. We have re-iterated the NICE Improving Outcomes Guidance on breast cancer (2002) with regard to mechanisms to promote continuity of care, in particular provision of a key worker. In many cases this role might be best filled by a specialist nurse.

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						cancer patients must have skills and knowledge in managing advanced breast cancer. The following quote from our survey summarises the specific challenge that many people with advanced breast cancer face: "The Hospice has been helpful. The breast care nurse 'disappeared' as soon as I received my secondary diagnosis. It was five months before I met anyone else with secondary breast cancer."	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.14	Full	44	1	Guidance on lapatinib and bevacizumab would be welcome. We appreciate that NICE have not yet finished appraising lapatinib through the technology appraisal process and the technology appraisal on bevacizumab had to be terminated. However, these agents are frequently used and receive a high level of media coverage. In this regard, direction on their efficacy and appropriate provision would be extremely helpful.	Lapatinib is the subject of a technology appraisal and therefore has not been covered in this guideline. We have discussed this in the background to the recommendation on p59. Similarly, bevacizumab was the subject of a technology appraisal until its recent termination. Therefore the guideline did not cover this.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.15	Full	44	36 & 44	The recommendations for endocrine therapy for patients with hormone receptor-positive advanced breast cancer are unclear and may result in confusion, particularly versions of the guideline which do not contain a summary of the supporting clinical evidence that may help to clarify the position. The potential confusion stems from the fact that the first recommendation states that "patients with hormone receptor-positive advanced breast cancer should be offered endocrine therapy as first-line treatment unless there is a clinical need to achieve a rapid tumour response," whilst the final recommendation recommends hormone receptor-positive patients should be offered endocrine therapy after chemotherapy. It appears the intended meaning is that, unless chemotherapy is used because of a clinical need to	We have amended the recommendation to avoid the potential confusion you have identified here.

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						achieve a rapid tumour response, endocrine therapy should be offered as a first-line treatment. This could be made more explicit by rewording the third recommendation. A possible alternative approach could be: "For patients with hormone receptor positive advanced breast cancer **who have received chemotherapy as their first line treatment, endocrine therapy should be offered following the completion of chemotherapy."**	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.16	Full	45	25	Breast Cancer Care and Breakthrough Breast Cancer feel that the importance of explaining to patients with advanced breast cancer the efficacy of hormone therapy could be emphasised more strongly in the guideline. In our experience, many people diagnosed with hormone receptor positive advanced breast cancer do not fully understand, and may not have been informed, that hormone therapy can be as effective as chemotherapy in managing their disease. Some patients have therefore expressed concern that they are not receiving what they perceive to be 'proper treatment' i.e. chemotherapy. It is essential that the benefits and risks of all treatments offered to patients are clearly explained so that patients are able to make informed choices about their care in partnership with their clinicians. NICE could therefore consider either adapting one of the existing recommendations or including an additional one to highlight the need to ensure patients are appropriately informed and involved.	We make general recommendations on information provision and support in Chapter 3 of the full guideline. We do not feel that additional recommendations are needed.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.17	Full	46	41	We know from our work with men with advanced breast cancer that they are often prescribed aromatase inhibitors (AIs). We propose that the draft guideline be revised to clarity the position regarding AIs and treatment of men with cancer, even if it is to	Unfortunately the very limited evidence available does not permit any clear conclusion about the effectiveness of AIs in this situation, either used alone or in combination with GNRH agonists. We have added a research recommendation to cover

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						acknowledge that there is not sufficient evidence to provide firm direction.	this.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.18	Full	51	2	The wording of this recommendation is ambiguous and may confuse readers. The recommendation states: "*Consider using combined 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."* Our view is that most patients would consider a greater probability of response as important. We suggest: "Consider using combination chemotherapy to treat patients with advanced breast cancer for whom a greater probability of response is thought to be desired and achievable and who understand and are likely to tolerate the additional toxicity".	We think the current wording is clear.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.19	Full	52	18	It is possible that the structure of the recommendations regarding systemic treatments may cause confusion for those implementing and using the final guideline. As the recommendations on chemotherapy have been separated from those on gemcitabine, it may not be clear to readers what role gemcitabine should play in the treatment pathway and when it should be used, particularly in relation to the sequencing of chemotherapy treatments; for example, what line of treatment gemcitabine should be considered as.	The recommendations on sequence of chemotherapy and gemcitabine have been separated because the former were written by the GDG and the latter were written by the technology appraisal team. We have clarified the use of gemcitabine in the qualifying statement on p53.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.2	Full	General		Breast Cancer Care and Breakthrough Breast Cancer have a specific over-riding concern about the appropriateness of using standard Quality-Adjusted Life Year (QALY)-based values for assessing the cost	This analysis was carried out in accordance with the methods set out in the current NICE Guidelines Manual and Methods Guide for Technology Appraisals.

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						effectiveness of new drug technologies in the palliative setting. This is because at best they may typically only achieve improved time to progression rather than significantly increased overall survival. However, when the average prognosis from secondary breast cancer is two years (BASO 2005), a six month improvement, whilst small, still represents a 25% gain. It is important that NICE fully considers how to determine what is cost effective and appropriate in relation to access to new drug treatments in the advanced cancer setting.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.20	Full	58	16	Please see comment 17 in relation to the need to clarify the place of gemcitabine in the patient pathway and its role in relation to chemotherapy treatment.	The recommendations on sequence of chemotherapy and gemcitabine have been separated because the former were written by the GDG and the latter were written by the technology appraisal team. We have clarified the use of gemcitabine in the qualifying statement on p53.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.21	Full	60	21	The draft guideline would also benefit from further information and explanation in support of the recommendation about trastuzumab.	We have amended the qualifying statement for this recommendation to clarify the reasons behind the recommendation
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.22	Full	72	7	Breast Cancer Care and Breakthrough Breast Cancer believe that the draft guideline may benefit from offering more detail regarding to the transition from active care to palliative care and support. We know from feedback from people affected by advanced breast cancer that lack of effective communication and coordination between health professionals during this process means that patients are often unclear, and sometimes mistaken, about the exact nature of palliative and supportive care. Many patients mistakenly understand palliative care to mean end of all treatment and imminent end of life. Patients are not always made aware of the wider	We feel these issues are adequately covered by the recommendations on p 73. We do not feel that more detail would be appropriate.

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						remit and potential long-term nature of palliative and supportive care services and as a result may not always access valuable services and support that help to improve their quality of life. There may also be some variation in access to the appropriate planning process for end of life care; 76% of patients who responded to our survey felt that they had not received the support they wanted in planning end of life care, compared to only 5% who had received this: "*There needs to be accurate advice and support about other people's experience of living with secondary breast cancer and functioning with it. Diagnosis brings the assumption that death is imminent, which thankfully is not always the case. Women should be able to have the assurance that not all is lost, otherwise in my experience it's easy to give up."* Some health professionals may need to improve the way that they manage the transition from active to palliative and supportive care. This includes ensuring that patients are properly informed about the implications for their individual treatment pathway, the practical support they will receive and how they can make the most effective use of the services and support available to them. In light of these concerns, the chapter on supportive and palliative care (chapter 5) could be expanded to include a discussion and a specific recommendation regarding the need, during the transition from active to non-active care, for open communication between health professionals and patients as well as coordination between individual health professionals and teams. This may also present an opportunity to more explicitly align this clinical guideline with the Department of Health's recent End of Life Care Strategy (2008), which specifically advocates open	

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						communication with patients and carers about these issues.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.23	Full	72	32	Breast Cancer Care and Breakthrough Breast Cancer support the recommendation for research to explore whether patients would prefer intravenous therapies to be delivered at home, near home or in the hospital setting. However, there will be a need for a high level of coordination, support and expertise to ensure that patients who prefer home- or community-based intravenous therapies are properly cared for and supported.	Thank you, we agree.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.24	Full	73	44	Breast Cancer Care and Breakthrough Breast Cancer welcome the inclusion within the guideline of a chapter on community-based treatment and supportive care. However, there is potential for the draft guideline to be strengthened in some areas to improve the quality of the experience of the patient with advanced breast cancer, as well as the effectiveness of health professionals' efforts to treat and support patients. Specifically, patients with advanced breast cancer may benefit from a breast care nurse, or another named key worker, to provide a similar style of support to that offered to primary breast cancer patients. Breast Cancer Care's Secondary Breast Cancer Taskforce would emphasise that the key worker needs to be a clinical nurse specialist with skills and knowledge in managing advanced breast cancer. However, surveys of breast care nurses carried out by Breast Cancer Care (2004) and Breast Cancer Care, Breakthrough Breast Cancer and the Royal College of Nursing (2007) indicate lack of time and knowledge may hinder these nurses from being able to provide adequate care to metastatic breast cancer	We have re-iterated the NICE Improving Outcomes Guidance on breast cancer (2002) with regard to mechanisms to promote continuity of care, in particular provision of a key worker. In many cases this role might be best filled by a specialist nurse. However, specifying who would be responsible for the role of key worker is a service issue and is beyond the remit of this clinical guideline.

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						patients. In the survey carried out in 2004 over 50% of nurses indicated that they would like training around managing the needs of metastatic breast cancer patients. In the follow up survey in 2007 again up to 50% of nurses reported they did not feel able to provide the quality of care to patients that they would like including the care provided to people with metastatic breast cancer. Breast Cancer Care and Breakthrough Breast Cancer would like the guideline to acknowledge that a key worker for all advanced breast cancer patients may have training/resource implications. Indeed, 52% of patients with advanced cancer who responded to our survey said that there were differences in the level of support they received compared to their experience with a diagnosis of primary breast cancer. In addition, 73% said that they did not have their needs for psychosocial, social, spiritual and financial needs assessed at diagnosis and over half (53%) said that they were not aware of what psychosocial support was available. This highlights the importance of having a named health professional to oversee care and answer questions. The work of Breast Cancer Care's Secondary Breast Cancer Taskforce recommend that this role must be undertaken by a nurse specialist who has skills and knowledge in managing advanced breast cancer. The following quotes from our survey reflect the wider experience of the support that people affected by advanced breast cancer receive. *"After primary diagnosis you are bombarded with support but after secondary diagnosis when you are under the care of the oncologist there seems to be lack of care. You are almost left feeling that there is not much point as it's too late to bother."*	This will be a matter for the Implementation team at NICE

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						"No support available on being diagnosed (with secondary breast cancer). Most definitely felt shunted into a siding and forgotten about as I didn't fit into the club' anymore (nobody wants to be in anyway)." Finally, although the NICE Supportive and Palliative Care Guidelines were published some time ago (2004), 75% of secondary breast cancer respondents to our survey said that they do not have a key worker assigned to them. In order to help address these implementation issues, NICE should consider strengthening the second recommendation that references the Supportive and Palliative care guidance to state: "Mechanisms should be developed to promote continuity of care, which **should** include the nomination of a person to take on the role of 'key worker' for individual patients."	As this text is a direct quote from another piece of NICE guidance we are not able to change the wording of this recommendation.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.25	Full	73	26	Although there is no UK evidence on provision of support for younger patients with families, there is some evidence from Australian studies which demonstrates the additional difficulties of younger women with advanced breast cancer, particularly when they have children. (Turner et al, 2005.) Our experience working with younger women with advanced breast cancer who have children tells us that have significant needs that are currently not effectively addressed. This includes providing support to their children during the course of their mother's illness and their subsequent bereavement. Patients on Breast Cancer Care's Secondary Breast Cancer Taskforce have also specifically highlighted the lack of support available for lone parents with advanced breast cancer.	We agree and have added a research recommendation on this.

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						We feel these areas are important for future research, particularly in relation to the additional support needs of family members at all stages of the patient pathway. Breast Cancer Care and Breakthrough Breast Cancer would welcome the inclusion of a recommendation in this area.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.26	Full	75	1	Breast Cancer Care and Breakthrough Breast Cancer welcome the inclusion of Chapter 6: *Management of specific symptoms.* We believe that the lack of awareness about symptoms and symptom management on the part of both patients and, in some cases, health professionals means that some patients may not receive the best treatment and support for their individual case and the inclusion of this issue in the draft guideline may help to address this. However, we would like to express some concern that this chapter does not include any discussion of liver or lung metastases. The liver and lungs are common sites for breast cancer metastases and so direction on the management of disease progression in these areas may be helpful. As part of this discussion, NICE could consider including, for example, surgery for isolated liver metastases, thermal ablation etc.	Thank you The scope of this guideline was very broad and it was not possible for the GDG to cover all of the topics within the limited development time. Stakeholders and the GDG therefore had to prioritise which topics the guideline would focus on. The GDG felt that there was very little that was specific to breast cancer in the management of liver and lung metastases so the topic was not considered a priority for investigation.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.27	Full	75	1	It could be helpful to include a section in this chapter regarding oncological emergencies that arise directly from advanced breast cancer, such as hypercalcaemia and superior vena cava obstruction. These are relevant to the advanced breast cancer patient and can occur at any time therefore direction on symptoms and appropriate action for patients as well as health professionals is essential. NICE should also consider including an explicit reference to the clinical guideline currently being produced regarding metastatic spinal cord compression (due for	The scope of this guideline was very broad and it was not possible for the GDG to cover all of the topics within the limited development time. Stakeholders and the GDG therefore had to prioritise which topics the guideline would focus on. The GDG felt that the issue of oncological emergencies was not unique to advanced breast cancer and therefore the topic was not considered a priority. We do not think that a reference to the NICE guidance on metastatic spinal cord compression is necessary.

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						publication in November 2008). A useful approach may be to follow the same approach for all symptoms as is adopted for uncontrolled local disease, which is to state: "The management of uncontrolled disease (*or fatigue/lymphoedema etc)* needs to be individualised and will usually involve a combination of treatments. A team approach is therefore important and will include nurses, surgeons, oncologists and psychosocial support."	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.28	Full	76	1	Breast Cancer Care and Breakthrough Breast Cancer welcome the inclusion of recommendations regarding the management of lymphoedema in the guideline, particularly as patients frequently tell us about the lack of adequate support for managing lymphoedema. From our discussion with health professionals we are also concerned that there may be a risk that patients who are affected by lymphoedema are not always identified and referred to specialist services. *'I was given minimal information (about lymphoedema) and even when I informed them of my intention to fly for 10 hours they did little to help me. By the end of my flight, I could not walk and it took three months to bring my arm back to a manageable size.' Online survey, 2008* These recommendations may help to improve and standardise services in this area.	Thank you
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.29	Full	76	20	The reference to input from a lymphoedema specialist is very welcome but, as stated above, in reality this can be a very under-resourced area. Patients frequently tell us that they do not have access to specialist support in this area. The draft	This is now covered in the recommendations on p76, line 37-38

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						guideline could be strengthened by including a reference to the need to provide patients with adequate support and information.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.3	Full	General		We also propose that the guideline explicitly state that age must not be a factor in offering treatment, unless significant co-morbidities mean a treatment is inappropriate or a patient is involved in a clinical trial investigating such issues. This would both support the right of patients to receive the most appropriate treatment for their condition and create consistency across both breast cancer guidelines by reflecting the recommendation made on this point in the guideline on early and locally advanced cancer (*Early and locally advanced breast cancer: diagnosis and treatment*, page 117, lines 30-33).	We agree that in general, age should not be a factor in offering treatment. However, in the very elderly there remains very significant concern amongst clinicians about the safety of using full doses of the more toxic chemotherapies and we believe this area needs to be researched before recommendations can be made.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.30	Full	76	25	We note that both the guideline for early and locally advanced breast cancer and the guideline for advanced breast cancer contain recommendations regarding lymphoedema. Whilst we believe this to be the correct approach, as lymphoedema can affect patients with any stage of the disease, the approaches taken in the two guidelines are very different. The early breast cancer guideline contains only a short section on lymphoedema diagnosis and management highlighting the potential effects of the condition and listing some broad treatment approaches for its management (e.g. skin care, compression garments). The recommendations are also very broad, highlighting the need for information provision and rapid access to services. However, the advanced breast cancer guideline contains far more detail on both the condition and its treatment, in particular relating to therapeutic approaches. It also makes much more specific recommendations as to how lymphoedema should be managed, including	Lymphoedema is generally more debilitating in patients with advanced breast cancer hence the advanced breast cancer guideline concentrates on the specific technical details of lymphoedema management.

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						specifying the use of complex decongestive therapy (CDT), and recommending providing information on support groups. While these recommendations are made in the context of advanced breast cancer, the guideline highlights the fact that "these recommendations are equally appropriate for the management of lymphoedema in patients with early breast cancer". Our survey of people affected by breast cancer has highlighted potential inconsistencies in access to, and standards of, lymphoedema services across the country, with 77% of respondents reporting that they were given information on lymphoedema and, of those who went on to develop symptoms, only 66% able to access services. Among those who did access services, many had difficulty in doing so. *"Once I persuaded the breast care nurse that I really did have a swollen hand and arm I did get a private consultation with a lymph nurse which was very useful and put my mind at rest."* Given the potentially debilitating nature of lymphoedema, its long term effects and the possible variations in services across the country, we feel it is important that recommendations made in this area are as clear, consistent and specific as possible. For these reasons, it may be beneficial for NICE to address the recommendations on lymphoedema to ensure consistency across both guidelines. It will be important to retain the patient-focused recommendations made in the early breast cancer guideline whilst ensuring that the advanced breast cancer guideline's detailed and specific recommendations on identifying and managing the condition are also included.	We agree this is potentially confusing so have deleted this sentence. We have also inserted a cross reference to the lymphoedema recommendations in the early breast cancer guideline.
SH	Breakthrough Breast Cancer	30.31	Full	78	13	Many patients with advanced breast cancer feel	Specifying who would be responsible for doing this

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	& Breast Cancer Care					disabled by fatigue, yet it is a symptom that is often neglected in terms of intervention and support: "*No support. I am a single mother whose children were 6 months and 3 years old when I was diagnosed (with advanced breast cancer) and received FEC chemo – I had to crawl through it."* Breast Cancer Care and Breakthrough Breast Cancer welcome the inclusion of a section on fatigue in the guideline. However, we feel it is important to provide clarity about which health professionals should be responsible for this assessment.	is a service issue and is beyond the remit of this clinical guideline. This will be a matter for local interpretation.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.32	Full	78	21	Breast Cancer Care and Breakthrough Breast Cancer welcome the recommendation for provision of timely information about and access to an exercise programme for all patients with advanced breast cancer who are experiencing cancer related fatigue. Patients with advanced breast cancer tell us that the availability of such services can be very limited and we support the efforts of the draft guideline to address this issue. However, cancer units do not typically provide this service. This is a service that is often provided by voluntary organisations, such as Breast Cancer Care. We propose that this recommendation be amended to include reference to services outside of the NHS and the importance of providing patients with information about how to access these services.	Thank you. We are not able to make recommendations that cover non-NHS providers.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.33	Full	79	39	Breast Cancer Care and Breakthrough Breast Cancer welcome the acknowledgement within the Guideline of the difficulties of the management of uncontrolled local disease and the recommendations made to address this. This is an especially distressing condition for those who are affected by it and one that has not received the attention it requires in relation to	Thank you

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						finding ways to treat and support those who are affected by it.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.34	Full	80	21	Breast Cancer Care and Breakthrough Breast Cancer fully support the recommendation for research into uncontrolled local disease and the possibility for the establishment of a national register. We would emphasise the urgency with which this research needs to be undertaken.	Thank you
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.35	Full	80	44	In relation to bone metastases, the guideline may need to reflect the likelihood that, in light of recommendations made in the early and locally advanced breast cancer guideline (*Early and locally advanced breast cancer: diagnosis and treatment*, page 82 lines 1-13), patients will increasingly receive adjuvant bisphosphonates. In particular, the implications for treatment when patients have already been exposed to these agents as part of their treatment of primary breast cancer should be considered.	Adjuvant bisphosphonates are not currently recommended by the "Early and locally advanced breast cancer" guideline.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.36	Full	84	4	With regard to brain metastases, we would suggest that the draft guideline highlight the need for neurological specialist input when considering treatment options.	We do not feel that this is necessary
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.37	Full	85	17	The clinical evidence cited in the draft guideline relating to the role of chemotherapy in the treatment of brain metastases, in particular leptomeningeal metastases, states that: '*Chemotherapy, including high dose intravenous methotrexate, appeared to be crucial in the treatment of leptomeningeal metastases and both intrathecal and intravenous chemotherapy improved patient survival.'* Given the strength of the evidence in relation to this	The previous wording overstated the strength of the evidence and has been revised.

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						issue, we would welcome clarification of the reason no recommendation has been made in this area.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.38	Full	85	26	We fully support the recommendation for research to compare stereotactic radiotherapy with whole brain radiotherapy. As well as the clinical efficacy issue, stereotactic gamma knife results in reduced hospital stays and significantly improves the impact of side effects. There is therefore potential for this treatment to offer patients improved quality of life as well as providing another approach to the treatment of an often debilitating form of metastasis.	Thank you
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.4	Full	General		There is inconsistency in the use of terminology throughout the draft guideline. In some instances the guideline uses the term 'advanced breast cancer' whereas in other instances the phrase 'secondary breast cancer' is used. Clarity may be improved if the draft guideline were to use one term throughout. However, should both terms be used in the final text we suggest that they are included in the glossary with a definition. At the moment, the term 'advanced' in included in the glossary but 'secondary' is not.	We have used the term "advanced" for clarity
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.5	Full	24	4	The draft guideline helpfully highlights the widespread lack of data available regarding advanced breast cancer in relation to incidence, prescribing and treatment patterns, ethnicity and socioeconomic status as well as primary care contact. As noted in the draft guideline, lack of data on incidence has also been raised by Breast Cancer Care's Secondary Breast Cancer Taskforce as a concern. In view of the anticipated increase in numbers of people living with secondary breast cancer together with the potential increase in numbers of people receiving more active as well as palliative treatment in the community, we believe that the following	Thank you We believe that this is covered by the current research recommendation on p72

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						should be promoted as a research priority: ▪ Relevant research organisations should be encouraged to undertake research to improve understanding of the benefits and challenges of management of advanced breast cancer in the community setting.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.6	Full	28	44	Breast Cancer Care's Secondary Breast Cancer Taskforce also highlighted concerns about Multi-Disciplinary Team (MDT) work in the context of advanced breast cancer. Many of the user representatives on the Taskforce report problems related to lack of continuity within the MDT team and lack of communication between team members. The outcome of this is that patients can feel that they need to co-ordinate their own care, for example by checking arrangements for scans and other tests. Breast Cancer Care and Breakthrough Breast Cancer therefore ask that the importance of effective MDT work, particularly in relation to disseminating information within the team and to the patient, be highlighted within the guideline.	This text is a summary of findings from the peer review of breast cancer teams in England (2004-2007) and therefore cannot be altered as you suggest.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.7	Full	31	9	It is helpful to include a list of symptoms that may be indicative of advanced breast cancer. However, while the symptoms that patients with advanced breast cancer may experience that are highlighted in the chapter are common the list is not exhaustive; for example, patients can experience other symptoms such as loss of appetite or unexplained weight loss. Additionally, there are currently no national guidelines on the identification and referral of patients with suspected metastatic breast cancer. The advanced breast cancer guideline therefore represents an important opportunity to offer patients and healthcare professionals support and information on identifying	This is not intended to be an exhaustive list and we therefore feel that the current text is appropriate as is. This text is only intended as background to the topic. It is not the purpose of this guidance to educate primary care professionals in the diagnosis of advanced breast cancer.

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						the symptoms of metastatic disease and ensuring patients are referred to specialist care at the earliest opportunity. This may be particularly helpful for primary care clinicians who may have limited experience of metastatic disease and to whom patients may present with symptoms. Feedback from Breast Cancer Care's Secondary Taskforce user representatives raised specific concerns about the lack of awareness amongst GPs about the significance of symptoms like bone-pain or other advanced breast cancer-related symptoms. Understandably, a balance needs to be achieved between providing patients with enough information to enable them to act on concerns without causing undue anxiety. However, as advances are made in the treatment of early breast cancer, more and more people will live disease free for longer periods of time and changes to follow-up practice will likely mean a greater emphasis on the role of primary healthcare professionals. These changes mean that it will be increasingly important for GPs to have an increased awareness of signs and symptoms of advanced breast cancer. In order to address the above concerns Breast Cancer Care and Breakthrough Breast Cancer propose that the chapter on presentation be revised as follows: ▪ To clarify the range of symptoms that may indicate a secondary breast cancer concern. ▪ To acknowledge the variation in pathways that patients may have to follow to obtain access to diagnostic tests – and set out preferred action in relation to referral to specialist breast units and/or specific tests	

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						that should be arranged by GPs where there is a concern related to advanced breast cancer. We also know from feedback from people affected by secondary breast cancer that there are wide variations in the time that it takes to get diagnostic tests arranged and completed. We would also welcome direction on suggested timeframes from the point of presentation of symptoms through to completion of investigations.	Specifying timeframes is a service issue and is beyond the remit of this clinical guideline. This will be a matter for local interpretation.
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.8	Full	31	13	It is helpful to include a list of diagnostic investigations and their appropriate use. However, it is important that the draft guideline is as explicit as possible regarding which healthcare professional should take responsibility for overseeing and organising tests and investigations in cases where a diagnosis of advanced breast cancer is suspected. Feedback from people affected by advanced breast cancer suggests that lack of coordination between healthcare professionals can result in some people experiencing long waits for tests to be organised, especially within the primary care setting, or for referral to a specialist centre for investigation. There are some concerns that the draft guideline may not address difficulties that could prevent patients from gaining timely access to diagnostic tests. Although we accept that a delay in diagnosis may not impact on prognosis, it can be very distressing for patients and may mean delays in treatments that offer relief from pain or other symptoms related to advanced breast cancer. Anecdotal evidence suggests that the longer the time between treatment for primary breast cancer and the occurrence of secondary breast cancer the greater	Specifying who would be responsible for doing this is a service issue and is beyond the remit of this clinical guideline. This will be a matter for local interpretation.

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						the likelihood of delay. This could be because GPs – or patients – are not aware of the implications of the symptoms experienced.	
SH	Breakthrough Breast Cancer & Breast Cancer Care	30.9	Full	33	23	We feel that the draft guideline could acknowledge more clearly the complexity of obtaining tissue samples from a metastasis in some areas (i.e. bone, brain etc) and provide some further direction about appropriate action.	We have suggested that a biopsy be obtained if feasible. The GDG expects that good clinical judgement will be applied to a decision as to the feasibility and appropriateness of obtaining a biopsy from any given site in the light of the clinical circumstances. Therefore we do not feel that a change is required to the recommendation.
SH	Breast Cancer Care	31				SEE COMMENTS FOR BREAKTHROUGH BREAST CANCER (ORDER NO 30) – JOINT RESPONSE	Thank you. Please see our responses to Breakthrough Breast Cancer
SH	Bristol Cancer Help Centre	32				This organisation was approached but did not respond.	
SH	Bristol-Myers Squibb Pharmaceuticals Ltd	33	Full	General		Bristol-Myers Squibb believes that the methodology used by NICE, with recommendations based on cost per QALY against an affordability threshold, works against the interests of patients with late-stage cancer. Purely economic calculations made in cases where the costs of keeping a sick person alive are high and life expectancy is low are unlikely ever to come out in favour of the patient.	This analysis was carried out in accordance with the methods set out in the current NICE Guidelines Manual and Methods Guide for Technology Appraisals. It is also worth noting that, in accordance with the current Guidelines Manual, the economic evidence is one of several criteria upon which the guideline development group base their final recommendations. Other factors they may take into account are fully explained in the 'qualifying statement'.
SH	British Association for Behavioural & Cognitive Psychotherapies (BABCP)	34				This organisation was approached but did not respond.	
SH	British Association for Counselling and Psychotherapy	35.0	Full	73	10	The guideline states that there are a range of local and national support services available, including counselling services. BACP would recommend that the guideline lists some services or places to find services to act as a guide for the health professional to refer the patient to. BACP have an information department, offering the public advice and information on counselling and providing details of counsellors in any specified area.	We are not able to cite specific services in the full guideline. However in the patient version of the guideline that will be produced there is a section where organisations providing information and support can be listed.

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SH	British Association for Counselling and Psychotherapy	35.1	Appendix 3	123 General		There is no definition in the glossary for psychological interventions, such as counselling and psychotherapy, which are described on page 73 under supportive care. BACP would recommend that the following definition is used: Counselling and psychotherapy are services sought by clients to help them resolve emotional, psychological and relationship issues within a context of guaranteed confidentiality and clear ethical boundaries using evidence-based practices to foster long-term recovery and increased wellbeing.	We feel that the term psychological intervention will be widely understood and therefore does not need further definition in the glossary.
SH	British Association of Art Therapists	36				This organisation was approached but did not respond.	
SH	British Association of Plastic Surgeons	37				This organisation was approached but did not respond.	
SH	British Dietetic Association	38				This organisation was approached but did not respond.	
SH	British Geriatrics Society	39				This organisation was approached but did not respond.	
SH	British Homeopathic Association	40				This organisation was approached but did not respond.	
SH	British Lymphology Society	41				This organisation was approached but did not respond.	
SH	British Menopause Society	42				This organisation was approached but did not respond.	
SH	British National Formulary (BNF)	43				This organisation was approached but did not respond.	
SH	British Nuclear Medicine Society	44				This organisation was approached but did not respond.	
SH	British Oncological Association	45				This organisation was approached but did not respond.	

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SH	British Psychological Society, The	46				This organisation was approached but did not respond.	
SH	British Society for Cancer Genetics	47				This organisation was approached but did not respond.	
SH	Bromley Primary Care Trust	48				This organisation was approached but did not respond.	
SH	BUPA	49				This organisation was approached but did not respond.	
SH	Calderdale PCT	50				This organisation was approached but did not respond.	
SH	Cambridge University Hospitals NHS Foundation Trust	51				This organisation was approached but did not respond.	
SH	Cancer Black Care	52				This organisation was approached but did not respond.	
SH	Cancer Network Pharmacists Forum	53				This organisation was approached but did not respond.	
SH	Cancer Research UK	54				This organisation was approached but did not respond.	
SH	Cancer Services Collaborative	55				This organisation was approached but did not respond.	
SH	Cancer Voices	56				This organisation was approached but did not respond.	
SH	Cancerbackup	57				This organisation was approached but did not respond.	
SH	Chartered Society of Physiotherapy (CSP)	58				This organisation was approached but did not respond.	
SH	Chephalon Ltd	59.0	Full	22	2	We note that the flowchart recommends offering anthracyclines to patients with no previous exposure to these agents and no contraindications to their use, yet the evidence for the use of anthracyclines at this stage does not appear to have been reviewed. As a consequence there is no guidance as to whether anthracyclines should be used as single agent or combination, and which combination would be most likely to provide the best benefit for response and	Use of anthracyclines is a long-standing standard practice in the management of patients with advanced breast cancer. Reviewing the evidence for this topic was therefore not considered a priority for investigation. This part of the pathway was included in the algorithm for completeness.

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						survival. For completeness, we would expect study data on anthracyclines in metastatic breast cancer to have been reviewed to support this recommendation.	
SH	Chephalon Ltd	59.1	Full	50	32-33	We are obliged to point out that, whilst doxorubicin and epirubucin are listed as examples of the anthracycline group of chemotherapeutic agents, no mention is made of the fact that there are different forms of individual anthracyclines (for example there are conventional and liposomal-encapsulated forms of doxorubicin). This is important as there are distinct differences between the forms relating to efficacy and safety. The points below highlight the differences between the efficacy and safety of liposomal-encapsulated doxorubicin (TLC D-99, Myocet) and conventional doxorubicin: • In a retrospective analysis of two phase III prospective randomised trials comparing liposomal-encapsulated doxorubicin with conventional doxorubicin in combination with cyclophosphamide and as single agents, respectively, for the treatment of metastatic breast cancer, 68 patients who had received prior adjuvant doxorubicin therapy were analysed. The analysis demonstrated a significantly higher objective response rate in the liposomal doxorubicin group (31% vs. 11%, P=0.04) and a significantly longer median time to treatment failure (TTF) in the liposomal-encapsulated doxorubicin group compared with conventional doxorubicin (4.2 months vs. 2.1 months, respectively [HR:2.06, 95% CI:1.18-3.61], log rank P=0.01 - Batist G *et al.* Anti-Cancer Drugs 2006; 17: 587-595). • Anthracyclines are the mainstay of treatment for metastatic breast cancer but their use is limited by cumulative dose-related cardiotoxicity and myelosuppression, despite long anthracycline-	We have not made any recommendations on the choice of anthracyclines and therefore do not feel it is necessary to list all the available anthracycline formulations in the background.

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						free intervals in many patients. Liposomal-encapsulated doxorubicin was developed to address these toxicity issues. • A phase III randomised, multi-centre trial compared liposomal-encapsulated doxorubicin (M) with conventional doxorubuicin (A), both at a dose of 60mg/m^2, in combination with cyclophosphamide (C) at 600 mg/m^2. Analysis of a subset of patients with recognised risk factors for cardiotoxicity indicated that these patients were more than 90% less likely to develop cardiac toxicity with MC relative to AC (Batist G *et al*. J Clin Oncol 2001;19(5): 1444-1454). • A meta-analysis of RCTs by the Cochrane Collaboration showed a significantly lower rate of both clinical heart failure and clinical and subclinical heart failure combined in patients treated with liposomal-encapsulated doxorubicin (RR = 0.20, 95% CI 0.05 to 0.75 and RR = 0.38, 95% CI 0.24 to 0.59 respectively). Based on this evidence, the authors concluded that in adults with a solid tumour liposomal-encapsulated doxorubicin should be favoured over conventional doxorubicin (van Dalen EC *et al.* Cochrane Database of Systematic Reviews 2006, Issue 4. Art. No.: CD005006. DOI: 10.1002/14651858.CD005006.pub2.). • In addition, a recently published review suggests that epirubicin cardiotoxicity may be higher than previously documented (Ryberg M *et al*. J. Natl. Cancer Inst. 2008; 100[15]: 1057-1067). In light of these points above, we request that the guidance should acknowledge the different forms of anthracyclines, as is the case with doxorubicin, since there are documented differences between them in	

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						terms of response and tolerability.	
SH	Chephalon Ltd	59.2	Full	50	38-42	We would support the statement about uncertainty and practice variation of sequential versus combination chemotherapy. • Liposomal-encapsulated doxorubicin at 60mg/m^2 is effective as first-line treatment in metastatic breast cancer in combination with cyclophosphamide at 600mg/m^2 (Batist G *et al*. J Clin Oncol 2001;19(5): 1444-1454). • Currently there is no standard therapy available for patients with metastatic breast cancer since the optimal combination of available treatments has not yet been established, though treatment options should be effective with minimal toxicity. Additionally, the optimal dosage schedule for many commonly used treatment regimens has not yet been established. Numerous clinical trials are being conducted using various combinations of chemotherapeutic agents in order to determine the optimal regimen for the treatment of advanced breast cancer. Whilst uncertainty about sequential or combination chemotherapy, optimal dosage and schedule remains, we would request that any guidance on chemotherapy for advanced breast cancer retains the flexibility to include new data on effective combinations of chemotherapeutic agents currently under study. • For example, preliminary data from the M77035 trial of trastuzumab, paclitaxel and liposomal-encapsulated doxorubicin show a high objective response rate of 93% in 54 patients and the combination was well tolerated when given as first-line treatment in advanced and metastatic breast cancer (Jakisch C. The Oncologist 2006;	Thank you The guideline will be reviewed at intervals, in accordance with NICE methodology, to determine if an update is required to take into account new evidence.

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						11[suppl 1]: 34–41)	
SH	Chephalon Ltd	59.3	Full	52	18-30	The definition of patient unsuitability for anthracyclines is unclear and we would request clarification. The wording in brackets suggests that patients who have had prior treatment with anthracyclines either in the adjuvant setting or as first-line therapy in metastatic disease are not suitable for anthracyclines. The implication from the definition and the qualifying statement below is that patients resistant to anthracyclines should not be re-treated with anthracyclines, either alone or in combination with other chemotherapeutic agents. We require clarification as to whether prior anthracycline exposure is synonymous with anthracycline resistance. • Objective responses have been observed in a retrospective analysis of 68 patients who had received prior adjuvant anthracycline therapy when they were treated with a liposomal-encapsulated formulation of doxorubicin plus cyclophosphamide as first line treatment of metastatic breast cancer (Batist G *et al.* Anti-Cancer Drugs 2006; 17: 587-595). Anti-tumour activity and time to treatment failure were significantly improved in patients receiving liposomal-encapsulated doxorubicin compared with patients who received treatment based on conventional doxorubicin for their MBC. The results of this study show that some patients who have received prior adjuvant anthracycline therapy might respond to subsequent re-exposure to liposomal doxorubicin in metastatic disease. Additionally, there are differences between contraindications of conventional and liposomal forms of doxorubicin. • For example, previous treatment with maximum	We have amended the text in brackets to make it clearer. We feel that there is insufficient evidence to make recommendations on the use of liposomal doxorubicin.

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						cumulative doses of anthracyclines or pre-existing heart disease are contraindications for conventional forms of doxorubicin but not for liposomal-encapsulated doxorubicin (doxorubicin SPCs, Electronic Medicines Compendium). Patients might therefore be denied the option of treatment with liposomal doxorubicin where it is possible that they could achieve an objective response.	
SH	Chephalon Ltd	59.4	NICE	General		We propose that changes to the full guidance document as a result of the proposed amendments listed above are also made to the NICE version of the guidance, where relevant	This will be done, in line with standard NICE procedures.
SH	Chugai Pharma UK Ltd	60				This organisation was approached but did not respond.	
SH	CIS'ters	61				This organisation was approached but did not respond.	
SH	Clatterbridge Centre for Oncology NHS Trust	62				This organisation was approached but did not respond.	
SH	Clinovia Ltd	63				This organisation was approached but did not respond.	
SH	College of Occupational Therapists	64.0	Full	general		The earlier the referral to Therapy the better, re faster discharge.	We agree with this statement.
SH	College of Occupational Therapists	64.1	Full	general		It would appear that there is very little mention of rehabilitation when in fact there should be more emphasis on it.	The issue of rehabilitation is an important one, unfortunately there is limited high-quality evidence available on this. We feel that we have drawn attention to rehabilitation issues as much as we are able to given the limited evidence.
SH	College of Occupational Therapists	64.10	Full	78	12	Recommendations occupational therapists have the skills re assessment and treatment of fatigue, and anxiety. Referral is key.	Specifying who would be responsible for doing this is a service issue and is beyond the remit of this clinical guideline. This will be a matter for local interpretation.
SH	College of Occupational Therapists	64.11	Full	80	41	Not only rehab. Need to look at abilities, maintaining functional independence and quality of life.	We feel that the statement about rehabilitation covers these issues.
SH	College of Occupational	64.2	Full	83	29-33	These are key functions of occupational therapists,	Referral to occupational therapy is covered in the

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	Therapists					and referral for Occupational Therapy is key in the treatment of breast cancer patients. Support and rapport need to be mentioned.	background on p 84, line 6.
SH	College of Occupational Therapists	64.3	Full	80	41	Rehabilitation is very important for these patients and this should be expanded to include examples such as provision of equipment to enable functional independence from OT.	This is a clinical guideline and as such cannot make recommendations on service provision issues.
SH	College of Occupational Therapists	64.4	Full	109	40	Occupational therapists would likely need to be involved with Packages 1 and 3 also.	The packages are artificial constructs designed for use in the model. There is no assumption that each individual will receive precisely this pattern of care, rather this was an attempt to estimate the costs of supportive care in general at this point in the patient pathway.
SH	College of Occupational Therapists	64.5	Full	84	19	Specialist Palliative care. The members of this team need to be listed, include OT.	This is a clinical guideline, not a service guideline.
SH	College of Occupational Therapists	64.6	Full	84	17	Active rehabilitation, includes functional assessment and treatment by OT.	We agree.
SH	College of Occupational Therapists	64.7	Full	125	16	Should add definition for OT in here.	We have not defined any other healthcare professional roles in the glossary and do not feel it is necessary to do this for OTs.
SH	College of Occupational Therapists	64.8	Full	73	1-6	Interesting points, crucial to have continued support both in hospital and community. End of life care should be noted. Patients need to have contacts in the community for support as required, and access to services re end of life care.	Thank you for your comments.
SH	College of Occupational Therapists	64.9	Full	75	24	Early identification and management of the swelling is CRUCIAL (not Important).	The wording is that agreed by the GDG and we do not feel this background information needs to be changed
SH	Commission for Social Care Inspection	65					
SH	Connecting for Health	66					
SH	Conwy & Denbighshire Acute Trust	67					

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SH	Co-operative Pharmacy Association	68					
SH	Countess of Chester Hospital NHS Foundation Trust	69					
SH	Craven Harrogate and Rural District PCT	70					
SH	Cytyc UK Limited	71					
SH	DakoCytomation Limited	73					
SH	David Lewis Centre	72					
SH	Department for Communities and Local Government	74					
SH	Department of Health	75.0	NICE (1.5.3.3)	80	1	End of life care policy colleagues wondered whether it would be helpful for section 1.5.3.3 to also include reference to social and spiritual support together with "psychological support", as it is at section 1.4.1.1	We do not think it is appropriate for a palliative care team to provide social and spiritual support. In 1.4.1.1 we are recommending various needs are assessed and do not think it would be the palliative care team that would do this.
SH	Department of Health	75.1	NICE (1.3.3.3)	52	18	In the key priorities for implementation, page 5, section 'systemic disease modifying therapy' the second bullet where text is in brackets doesn't seem to make sense: (adjuvant anthracyclines or first-line metastatic anthracyclines, or contraindicated). We would bne grateful for clarification.	We have amended this text to make it clearer.
SH	Department of Health	75.2	NICE (1.1.2.1, 1.1.2.2)	34-35	46-1	Monitoring disease progress, we are in agreement with the 2 noted 'do nots' but we would find that a few bullets to advise on what imaging to use to monitor response to treatment would be appropriate before the 2 bullets advising what not to do. Eg CT/US for metastatic liver disease etc.	The GDG did not feel that it was possible to make recommendations on what imaging modalities should be used to monitor disease progress, or with what frequency because there would be wide variation in imaging requirements depending on the clinical circumstances. The recommendations that were made were intended to avoid inappropriate routine use of these two modalities.
SH	Department of Health, Social Security and Public Safety of Northern Ireland	76				This organisation was approached but did not respond.	
SH	Derby-Burton Cancer Network	77				This organisation was approached but did not respond.	
SH	Doncaster PCT	78				This organisation was approached but did not respond.	

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SH	East & North Herts PCT & West Herts PCT	79				This organisation was approached but did not respond.	
SH	Eisai Limited	80				This organisation was approached but did not respond.	
SH	Eli Lilly and Company Limited	81				This organisation was approached but did not respond.	
SH	Essex Cancer Network	82				This organisation was approached but did not respond.	
SH	Faculty of Public Health	83				This organisation was approached but did not respond.	
SH	GE Healthcare	84				This organisation was approached but did not respond.	
SH	General Practice and Primary Care	85				This organisation was approached but did not respond.	
SH	GlaxoSmithKline UK	86.0	NICE (1.1.2.1, 1.1.2.2)	34-35	46-1	There appears to be no guidance on appropriate monitoring techniques and frequencies. The only recommendations refer to techniques which should not be employed. It would be helpful to have more guidance on this subject.	The GDG did not feel that it was possible to make recommendations on what imaging modalities should be used to monitor disease progress, or with what frequency because there would be wide variation in imaging requirements depending on the clinical circumstances. The recommendations that were made were intended to avoid inappropriate routine use of these two modalities.
SH	GlaxoSmithKline UK	86.1	NICE 1.3 FULL 4.3	10-11 58-61		The shorter NICE guideline does not mention lapatinib and other biological response modifiers for which NICE guidance is either currently or shortly available. We suggest that omitting to mention these therapies, whether recommended by NICE or not, does not fully address current treatment options. Furthermore, this is inconsistent with other areas of the guideline, e.g., the section covering endocrine therapies (1.3.2), which addresses interventions such as aromatase inhibitors which have not been specifically approved by NICE in advanced breast cancer.	The NICE version only contains the recommendations made in the guideline, it does not contain background information. Lapatinib is the subject of a technology appraisal and therefore has not been covered in this guideline. We have discussed this in the background information on p59. Therefore this information on lapatinib is not present in the NICE version.
SH	GlaxoSmithKline UK	86.2	FULL 4.3	60 61	27-49 1-14	This section reviews the evidence for treatment in patients undergoing therapy with a biological	Lapatinib is the subject of a technology appraisal and therefore has not been covered in this

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						response modifier who experience disease progression. However, the review addresses only trastuzumab, which is unlicensed in this setting, and omits evidence for lapatinib, which is the only drug specifically licensed for use in these patients. We suggest that details of study EGF100151* are included for completeness. * Cameron D, Casey M, Press M, et al. A phase III randomised comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on tratsuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008; epub ahead of print publication)	guideline.
SH	GlaxoSmithKline UK	86.3	NICE 1.3.4.1	59		The indication stated for trastuzumab is incorrect in stating that combination trastuzumab is only licensed with paclitaxel. Trastuzumab is also licensed in combination with docetaxel for the treatment of those patients who have not received chemotherapy for their metastatic disease, as well as in combination with an aromatase inhibitor in postmenopausal patients with hormone-receptor positive metastatic breast cancer not previously treated with trastuzumab. We suggest that the text is modified for accuracy.	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines. TA34 was published in 2002, at which time the statement regarding the licensed combinations for trastuzumab was correct, although we acknowledge that this is no longer the case. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	GlaxoSmithKline UK	86.4	FULL 4.3	59	25-26	The current wording would be clearer if it were explicit about referring to NICE approval. Currently it could be misinterpreted as referring to regulatory approval.	We have amended the text to clarify this is about NICE approval.

SH	GlaxoSmithKline UK	86.5	FULL 4.3	59	33-36 and 44 - 45	The indication statement in the recommendation is inconsistent with the text in lines 33-36 regarding the licensing of trastuzumab in combination with docetaxel. Additionally, as above, there is no mention of the additional licensed indication for trastuzumab in combination with an aromatase inhibitor. We suggest that the text is modified for accuracy.	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines. TA34 was published in 2002, at which time the statement regarding the licensed combinations for trastuzumab was correct, although we acknowledge that this is no longer the case. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	GlaxoSmithKline UK	86.6	FULL	59	40-42	The GDG have recommended that a technology appraisal is conducted to investigate the clinical and cost effectiveness of the trastuzumab and docetaxel combination. We suggest that the GDG also considers the trastuzumab/aromatase inhibitor combination for technology appraisal.	We stress that it is not standard practice for the GDG to suggest which topics should be investigated by technology appraisal. This was an exceptional circumstance because the GDG were tasked to update TA34 in the guideline but were not able to do so because of the limited clinical data available. We should also stress that the GDG do not have any influence on which topics eventually get investigated as TAs – these decisions are made by the NICE topic consideration panels. Trastuzumab in combination with AIs is on the list of topics being considered by the NICE Topic Selection Panel for Cancer as a future STA. We have therefore not investigated this combination within the guideline.
SH	GlaxoSmithKline UK	86.7	NICE (1.3.4.4)	60and p22 Chemotherapy algorithm	21	The recommendation that trastuzumab should not be continued after disease progression outside the CNS implies that it can be continued if progression is restricted to the CNS. We suggest that this is made explicit in the algorithm on page 30, which currently only mentions extracranial disease progression.	We have amended the recommendation to clarify that trastuzumab should not be discontinued if disease progression is within the CNS alone. We do not feel that changes to the algorithm are needed.

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SH	GlaxoSmithKline UK	86.8	NICE (1.3.2, 1.3.4)	46-47 59-60 pp21 and 22 algos	38-20 43-25	The recommendations and algorithms for endocrine therapy and chemotherapy do not consider the population of 'co-positive' patients who express hormone receptors and over-express ErbB2/HER2 receptors. The choice and sequencing of treatments in these patients requires careful consideration and as such we suggest that guidance specifically addressing this profile would be helpful.	There is insufficient evidence on this group of patients to enable recommendations to be made at this time.
SH	Gloucestershire Acute Trust	87				This organisation was approached but did not respond.	
SH	Good Hope Hospitals NHS Trust	88				This organisation was approached but did not respond.	
SH	Greater Manchester and Cheshire Cancer Network	89				This organisation was approached but did not respond.	
SH	Guerbet Laboratories Ltd	90				This organisation was approached but did not respond.	
SH	Guys and St Thomas NHS Trust	91				This organisation was approached but did not respond.	
SH	Hampshire & Isle of Wight Strategic Health Authority	92				This organisation was approached but did not respond.	
SH	Harrogate and District NHS Foundation Trust	93				This organisation was approached but did not respond.	
SH	Healthcare Commission	94				This organisation was approached but did not respond.	
SH	Heart of England Acute Trust	95				This organisation was approached but did not respond.	
SH	Help the Hospices	96				This organisation was approached but did not respond.	
SH	Hinckley & Bosworth Primary Care Trust	97				This organisation was approached but did not respond.	
SH	Humber and Yorkshire Coast Cancer Network	98				This organisation was approached but did not respond.	
SH	Imaging Equipment Ltd	99				This organisation was approached but did not respond.	
SH	Independent Healthcare Advisory Services	100				This organisation was approached but did not respond.	

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SH	Institute of biomedical Science	101				This organisation was approached but did not respond.	
SH	Intra-Tech Healthcare Ltd	102				This organisation was approached but did not respond.	
SH	Johnson & Johnson Medical	103				This organisation was approached but did not respond.	
SH	L'Arche UK	104				This organisation was approached but did not respond.	
SH	Launch Diagnostics Limited	105				This organisation was approached but did not respond.	
SH	Leeds PCT	106				This organisation was approached but did not respond.	
SH	Leeds Teaching Hospitals NHS Trust	107				This organisation was approached but did not respond.	
SH	Leicestershire Northamptonshire and Rutland Cancer Network	108				This organisation was approached but did not respond.	
SH	Lilly UK	109				This organisation was approached but did not respond.	
SH	Liverpool PCT	110				This organisation was approached but did not respond.	
SH	Liverpool Womens NHS Foundation Trust	111				This organisation was approached but did not respond.	
SH	Long-term Conditions Alliance	112				This organisation was approached but did not respond.	
SH	Luton & Dunstable Hospital NHS Foundation Trust	113				This organisation was approached but did not respond.	
SH	Lymphoedema Support Network, The	114	Full	General		The LSN are delighted that the problem of lymphoedema in advanced disease has been so well addressed in the NICE draft guidelines, we hope that the guidelines will help support the diagnosis, treatments and information provision for patients with the condition.	Thank you
SH	Macclesfield District General Hospital	115				This organisation was approached but did not respond.	

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SH	Macmillan Cancer Relief	116				This organisation was approached but did not respond.	
SH	Maidstone and Tunbridge Wells NHS Trust	117				This organisation was approached but did not respond.	
SH	Marie Curie Cancer Care	118				This organisation was approached but did not respond.	
SH	Medical Deivce Innovations Ltd	119				This organisation was approached but did not respond.	
SH	Medical Solutions	120				This organisation was approached but did not respond.	
SH	Medicines and Healthcare Products Regulatory Agency (MHRA)	121				This organisation was approached but did not respond.	
SH	Merck Pharmaceuticals	122				This organisation was approached but did not respond.	
SH	Mid Staffordshire General Hospitals NHS Trust	123				This organisation was approached but did not respond.	
SH	Milton Keynes PCT	124				This organisation was approached but did not respond.	
SH	National Association of Assistants in Surgical Practice	125				This organisation was approached but did not respond.	
SH	National Audit Office	126				This organisation was approached but did not respond.	
SH	National Cancer Network Clinical Directors Group	127				This organisation was approached but did not respond.	
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer	128.0	Full	General		The Guidelines should draw attention to those parts that are based on "expert opinion" as areas that should form the basis of local guidelines. These might be subject to further research and audit to refine future guidelines. In addition the Guidelines should return to a format which has the level of evidence made clear.	Recommendations which are based on expert opinion alone are identified in the qualifying statements. It is not clear in what way you feel the guidelines are not helpful. However the decision no longer to grade recommendations in guidelines was taken by NICE in 2006 after a period of public consultation.

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	Physicians					Guidelines should be that and no more - a useful guide for local protocols. They need interpreting and, if they are to be useful, should be either firmly evidence based or explicitly pragmatic. They will be used by clinician if they are felt to be helpful. Unfortunately, as currently written the NICE guidelines do not seem to have quite achieved that.	The main reason was that the old system purely reflected the quality of therapy studies and neither the importance of the recommendations nor the quality of diagnostic or safety studies. There could be a very important recommendation which was not and might never be supported by RCT evidence. Also there was a tendency for Grade A recommendations to be implemented first, which might be inappropriate. The full version of these guidelines contains brief 'qualifying statements' which explain how and why the GDG made the recommendations and give more information than a simple grade would. NICE is also piloting a system of making links between evidence and recommendations more explicit and this will be used in the future. These are guidelines for the NHS in England and Wales and so the expectation is that health professionals and teams will use them to shape their clinical practice. They are of course only guidelines and not mandatory, and so if people choose to use other sources of guidance, then they would be expected to be able to justify that decision to their trust and local commissioners. Support for implementing these guidelines will be available in the form of implementation tools which will be published along with the guideline.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.1	Full	General		At times the guidelines focus on clinical data, and at others on health economic aspects - but not consistently so.	NICE has a responsibility to make recommendations as far as possible based on evidence of cost effectiveness as well as clinical effectiveness. It would not be possible for all the questions in a clinical guideline to be subject to health economic analysis – there is neither the time nor the resources. The GDG and the NCC team have to make a pragmatic decision about which questions to address. So, a few of the recommendations are based on an assessment of cost effectiveness but the majority on clinical

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						At times they restrict their recommendations to licensed indications, while in some situations they reject licensed indications (docetaxel-herceptin) and at other times recommend unlicensed treatments. There is a need to be totally consistent here, and if the conclusion is that the Guidelines cannot recommend unlicensed indications for legal reasons, then there needs to be a clear statement to that effect at the beginning. This will however seriously reduce the utility of these documents. At times one feels that some things are supported or not supported on purely health economic reasons - I think the guidance needs to be much clearer when it is the health economics that drives a recommendation rather than pure clinical data.	effectiveness alone. This explains the apparent inconsistency you noticed. NICE clinical guidelines are able to recommend the use of drugs outside their licensed indication and therefore they do not restrict their recommendations on the basis of license. However, there must be very good evidence of effectiveness to support making these recommendations. There is also no obligation to recommend a drug or combination within the licensed indication. The qualifying statements make clear when cost effectiveness was formally assessed and informed the recommendations. NICE has a responsibility to make recommendations as far as possible based on evidence of cost effectiveness as well as clinical effectiveness. It would not be possible for all the questions in a clinical guideline to be subject to health economic analysis – there is neither the time nor the resources. The GDG and the NCC team have to make a pragmatic decision about which questions to address. So, a few of the recommendations are based on an assessment of cost effectiveness but the majority on clinical effectiveness alone. This explains the apparent inconsistency you noticed.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council	128.10	Full (1.1.1.3)	31	39-41	Plain radiographs of hot spots on a restaging bone scan should be preformed to identify sites at risk of fracture.	We believe that such a recommendation is too prescriptive, as in some circumstances it will be clear from bone scintigraphy.

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	Clinical Oncology/ Association of Cancer Physicians						
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.11	Full (1.1.1.4)	31	42-44	Biopsy of solitary equivocal lesions should be considered.	Guidelines are intended to cover the majority of clinical situations, not all possible situations. We feel that the situation you describe would be unusual and therefore the guideline does not make recommendations on this. In unusual situations such as this we would expect clinical judgement to be used.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.12	Full (1.1.1.6)	33	9-11	Re-biopsy of patients – this is a bit rigid and there are patients who change status – surely clinical judgment should be used here to say that if the pattern of disease is different to what should be expected from the primary status, then rebiopsy can be considered? There is evidence to show that changes in ER and Her 2 status occurs in 20-25% of patients between the primary tumour and development of metastasis, with changes occurring in either direction (+ to – and – to +)	This document is a guideline and not a mandatory approach to clinical practice. As such it does not replace clinical judgement. The evidence in this area is observational and of variable quality. The GDG did not feel that it warranted a recommendation, which would be a substantial change to current practice. These issues have been identified in the qualifying statement that accompanies this recommendation in the full version
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer	128.13	Full (1.1.2)	34-35	46-4	The guidelines indicate what should not be done but does not provide guidance on what should be done to assess response. Regular symptom evaluation and follow-up imaging with CT and/or plain radiographs recommended every 8-12 weeks.	The GDG did not feel that it was possible to make recommendations on what imaging modalities should be used to monitor disease progress, or with what frequency because there would be wide variation in imaging requirements depending on the clinical circumstances. The recommendations that were made were intended to avoid inappropriate routine use of these two modalities.

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	Physicians						
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.14	Full (1.2.1.1)	40	26-27	We support the need to ensure the support needs for families are considered and the requirements to regularly reassess patients' needs as circumstances change.	Thank you
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.15	Full (1.3.1.3)	44	44-45	Routine use of hormone therapy post chemo - this will be controversial as it is largely a data-free zone (though it is my own practice). This unreferenced statement also intrigues me:	This recommendation was based on GDG consensus, as stated in the qualifying statement. The GDG believes that this is current accepted UK practice.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.17	Full (1.3.2.4)	47	16-17	In tamoxifen failures, men should be treated with goserelin plus an aromatase inhibitor rather than an aromatase inhibitor alone.	We presume this refers to the report by Giordano and Hortobagyi (Journal of Clinical Oncology, Vol 24, No 21 (July 20), 2006: pp. 42e-43.) We feel that a case series of 2 patients is an inadequate basis for making a recommendation
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National	128.18	Full (1.3.3.3)	52	18-25	We have very fundamental concerns in using the limited data that are available to try and derive the optimal sequence of chemotherapy for advanced	We make no claims to have identified the most clinically effective sequence of chemotherapeutic agents. It is disappointing that so little of the data

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	Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians					breast cancer. Firstly, to the best of our knowledge, none of the trial datasets used placed any restrictions on the use of post-progression chemotherapy. Thus using the OS data from these studies to model outcome in a treatment sequence approach seems flawed – since one cannot remove from the published data the effect of the subsequent therapies. Same issue about weekly taxol as in the early guidelines - it is used and is more effective than three-weekly - it would be better to say that three weekly taxol single agent appears to be the least effective way of giving a taxane and should be avoided. The sequence of chemotherapy seems over rigid - there are no good data that there is an optimal sequence, and for many patients it may not be appropriate to start with full dose docetaxel, and the use of a gentler agent like vinorelbine or Capecitabine may be more appropriate. The text implies that the argument for this sequence is based on pure health economics with large uncertainties which seems a dangerous basis for issuing national guidance, particularly when they do not define the dose of docetaxel and there is a randomised trial showing differences in both efficacy and toxicity for different doses! Would be much better to recommend that each oncology centre, network has an agreed systemic therapy protocol that is reviewed on an annual basis rather than a restrictive, non evidence based sequence of treatments.	that is required to perform adequate cost-effectiveness analysis is collected and published from large randomised trials. We invite the NCRI to consider what might be done to rectify this very important gap in the information available for NHS decision making. We acknowledge there is clinical effectiveness data supporting the use of weekly paclitaxel. Unfortunately the necessary information from the Will Weekly Win trial was not available in time to be included in the health economic analysis. The recommended dose of docetaxel in breast cancer is 100mg/m2. This guideline is intended to cover the majority of clinical situations but is not a mandatory approach to clinical practice. As such it does not replace clinical judgement. We are aware of the limitations of the health economic analysis used. We believe this is the most thorough health economic analysis of the chemotherapeutic management of advanced breast cancer yet performed. We hope that with better information in the future, better analyses will be possible. It is reassuring that the analysis has come up with a sequence of treatments that closely mirrors much contemporary, routine practice. The Department of Health has asked NICE to produce guidelines on the management of advanced breast cancer.

SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.19	Full (1.3.4.1)	59-60	44-2	HER2 therapy. We don't understand why they don't support docetaxel+Herceptin when there are more HER2 3+/FISH+ patients in that RCT than the paclitaxel-herceptin trial - sometimes arguments for and against including studies do not make sense.	This recommendation is from 'Guidance on the use of trastuzumab for the treatment of advanced breast cancer', NICE technology appraisal guidance 34 (2002).The recommendations from TA34 were formulated as part of that technology appraisal and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendations can be found at www.nice.org.uk/TA034. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.2	Full	General		Additionally updating local guidelines can occur as and when necessary. National Guidelines will inevitably be "behind the times" in some areas.	The guideline will be reviewed at intervals, in accordance with NICE methodology, to determine if an update is required to take into account new evidence.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.20	Full (1.3.4.4)	60	21-22	HER2 therapy beyond progression - we have two randomised trials both showing DFS/TTP advantage (small GBG study with Herceptin, and larger Lapatinib one). So why such a rigid statement about not continuing anti-HER2 therapy beyond progression? - is this purely health economics – if so, this should be stated. There are better data for doing this than some other things not supported, such as giving docetaxel to all as first line therapy, annual mammography in follow-up or the use of Capecitabine after vinorelbine (and vice versa). Indeed, they seem to us to use inconsistent standards of level of evidence for some of their	Trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data. The guideline recommends that docetaxel be offered first line following anthracyclines. This is not a recommendation that all patients receive docextaxel as guidelines are not a mandatory approach to clinical practice and as such do not replace clinical judgement. If the clinical judgement is that docetaxel should not be used then it should not be used.

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						statements in both documents - with strong support for some things with little supportive data and weak or non-existent support for things where there are data. There is clearly good evidence that HER2-targeted therapy is effective beyond failure of trastuzumab. This includes 2 randomised trials - the GBG26 study with trastuzumab-capecitabine and the EGF100151 study with lapatinib-capecitabine. There are in addition a number of non-randomised studies including studies not identified by the ERG that support continuing trastuzumab in combination with additional chemotherapy. The relative merits of lapatinib and trastuzumab in this setting are not established and whilst the health economics of lapatinib are the subject of a separate STA, the current guidance has not considered the health economics of continuation trastuzumab. Whilst this may be a reason to reject trastuzumab, the claim that there is no evidence to support continuation trastuzumab seems not to be fully justified.	Lapatinib is the subject of a technology appraisal and therefore has not been covered in this guideline. We have discussed this in the background to the recommendation on p59. We have changed the text to accurately reflect the level of evidence.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.21	Full (1.5.1)	75	3	Lymphoedema again features as the top concern in symptom control for advanced cancer. This we believe is wrong – fatigue and pain are much more common and there is nothing on breathlessness which is in our experience considerably more common that lymphoedema. If this section is to be comprehensive then we need to cover all the common symptom areas!	The order of the sections in this chapter is not intended to convey their level of importance. The scope of this guideline (diagnosis and treatment of patients with advanced breast cancer) was very broad and it was not possible for the GDG to cover all of the topics within the limited development time. Stakeholders and the GDG therefore had to prioritise which topics the guideline would focus on, so this section is not intended to be comprehensive.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/	128.22	Full (1.5.3)	79-80	45-5	We would like to see guidance about regional recurrences - for example in the pectoral muscles, lymph nodes under the breastbone and between the ribs, in the supraclavicular nodes and in the nodes surrounding the neck. We understand it is relatively uncommon, but we believe that patients in this	The management of locoregional recurrence, other than uncontrolled local disease, is outside the scope of this guideline. This is a relatively common situation for which curative interventions may be possible.

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	Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians					situation can feel that they don't fall naturally into either locally advanced or advanced breast cancer and find this isolating.	
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.23	Full (1.5.4)	80-81	43-7	There is no discussion on when to start bisphosphonates and duration of therapy. Importance of dental care and avoiding invasive dental procedures to minimise risk of osteonecrosis of the jaw needed. No reference to the zoledronate v pamidronate data which does suggest an advantage for zoledronate over pamidronate.	The revised recommendation is to consider offering bisphosphonates to patients newly diagnosed with bone metastases. If bisphosphonates are not offered at this point it will be a matter for clinical judgement to decide when they are offered. There is no direct comparative evidence on which to base a recommendation on treatment duration and this will be a matter for clinical judgement. We agree that this is important but do not feel that this level of detail is appropriate. As we state in our qualifying statement for the recommendation on p81 (line 2-4), there was no strong evidence of comparative clinical effectiveness for any of the bisphosphonates. In addition there was conflicting health economic evidence over which bisphosphonate was the most cost-effective, although as a class of drugs they do seem to be cost-effective. The GDG therefore felt that it was not possible to recommend a specific bisphosphonate. Rosen et al. 2004 is retrospective sub-group analysis of data from Rosen et al. 2001. Rosen et al. 2001 was an equivalence study of 1500 patients. It only recruited 1100 patients so was underpowered and was only designed to show equivalence of the interventions. Therefore the GDG do not feel that this trial can be used as the basis for changing the recommendation as you suggest.

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SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.24	Full (1.5.4.3)	81	9-12	Fractionated radiotherapy should be considered in patients with a single bone metastasis where disease control is an aim of treatment. Fractionated radiotherapy is appropriate after orthopaedic fixation of bone and the field should include the whole prosthesis/implant/stabilising structure.	The situation you describe relates to a situation in which treatment intent would be disease control rather than pain management. Our recommendation concerns pain control and we therefore do not think that any changes are needed.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.25	Full (1.5.4.4)	81	14-16	In line with NICE provisional guidance for spinal cord compression (SCC), all patients with significant vertebral metastasis or at risk for SCC should be assessed but a spinal/orthopaedic surgeon	This recommendation is about long bones and hence is not covered in the SCC guideline. We have deliberately not covered SCC issues here as we were aware that the SCC guideline was in development.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.26	Full (1.5.5)	84	11-22	No mention of gamma-knife/ stereotactic XRT, no mention of the use of systemic therapy to treat brain metastases. Option of radiosurgery in patients who would be considered for surgery (< 3 mets, controlled systemic disease, good PS) but who have surgically inaccessible lesions should be included. This population is likely to increase with better systemic treatment options. Ii. Role of WBRT following radiosurgery or surgery is still debated, it clearly contributes to local control but little if anything to OS. The risk/benefit of WBRT wrt cognitive decline vs local tumour recurrence in	This comment refers to an extremely small group of patients. There is little or no data about the management of this precise situation and it is not covered in the guideline. For stereotactic radiosurgery in general, the GDG felt that the quality of the data was not sufficient to make a more general recommendation about its use at this time, but a recommendation for further research has been made. On the basis of the currently available data, the GDG feels that its current recommendation is appropriate. Clearly this may need to be reviewed in future if new evidence is published.

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						relatively good prognosis patients is still unknown.EORTC 22952 addresses this (across all histologies) and will report in 2009. We would not want to see a blanket recommendation for WBRT without seeing these data. The evidence for the routine use of post-surgical WBRT rather than WBRT on relapse seems to be rather limited and is surely an intervention that requires further research.	
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.27	Full	50	14-17	Very unlikely that the sequence of endocrine treatments is of any great importance and trials comparing different sequences would be of minimal value.	There is currently no evidence to inform a choice of endocrine agent after failure of 3rd generation aromatase inhibitors. We feel research to fill this gap is important.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.28	Full	58	25-28	The efficacy of chemotherapy agents in advanced disease that have previously been used in the adjuvant setting (re-challenge) requires investigation. As increasingly more adjuvant chemotherapy is used this has become a high priority. As stated in 4.4 this also applies to anti HER2 therapy where retreatment with trastuzumab should be compared with lapatinib or an alternative HER2 targeted treatment.	We accept that there has recently been some interest in this area but there was no GDG consensus that this is a high priority for research. We are pleased that the need for further studies in relation to retreatment with trastuzumab compared with other HER2 targeted treatments is seen as a research need by the NCRI Clinical Studies Group. Evaluation of cost-effectiveness must be central to the design of any such trial.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of	128.29	Full	61	10-11	This has already been the subject of an RCT which has reported recently (GB-26) Whilst such a trial would undoubtedly add to the limited amount of available evidence, its cost effectiveness would be limited. It would be a very	The reported studies are small. The GBG-26 study has yet to demonstrate a statistically significant improvement in overall survival. Cost-effectiveness data from these studies has yet to be made available. At this point it is not possible to know if the data that will be made available from these

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	Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians					expensive study that is unlikely to generate radically different results to those from the existing trials but would eat into the limited pot of money available to conduct cancer trials as industry sponsorship is highly unlikely. A health economic analysis based on existing trial data might be a better approach.	studies will be adequate to perform good quality cost-effectiveness analysis. Trastuzumab is an extremely high cost treatment and it would be inappropriate for patterns of use to change until adequate research demonstrating its cost effectiveness has been performed. We have amended these research recommendations to include collection of data required for prospective cost effectiveness analysis.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.3	Full	General		Although there is a section on research recommendations, there is little emphasis on the importance of clinical trial participation or support of the NCRN research agenda. The role of the research nurse is not mentioned. The importance of providing a comprehensive research portfolio and making treatment within clinical trials the standard of care should be made clear.	We acknowledge the importance of clinical trials participation, however it is not the purpose of NICE guidelines to support the NCRN research agenda. The role of the research nurse is a service issue and outside the remit of this clinical guideline.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.30	Full	80	22-24	The role of local therapy in patients presenting with metastatic disease should be evaluated. Retrospective studies indicate the value of RT or surgery but no prospective data exist.	We feel that our current research recommendation would encompass the research you suggest.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network	128.31	Appendix 1	General		There are a lot of specific concerns, many of which were not addressed in the limited decision tree modelling. The use of 4 or 5 significant figures in some of the parameters is bizarre, given the very	The model structure using a decision tree design was deliberately kept simple due to the multitude of treatment options being compared in the one economic model.

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	NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians					crude estimates of some of the key data. It suggests a belief in a need for precision in the modelling which is not justified by the available data.	Without page references it is not clear exactly which figures are being referred to. The use of an indirect treatment comparison involved making a number of assumptions, but gave us very detailed outputs from the statistical model. In the spreadsheet the numbers were not rounded up, but were presented in the report to perhaps too many significant figures. Since all interventions were assessed in the same way this will not alter the results, but could mislead the reader. However the figures are now reported more appropriately.
						Furthermore, the only models run use 3-weekly paclitaxel or docetaxel as the first line. Many of us might use weekly paclitaxel, or in some circumstances, rechallenge with anthracyclines or for more indolent disease use Capecitabine. Clearly the model would get very complex if they were to do this – but then the model is going to have limited utility if it assumes that only 3-weekly taxanes can be used first line. We see no need, and indeed some risks, in driving a national prescription for chemotherapy for advanced breast cancer using such an uncertain economic model based on datasets from trials designed with entirely different purposes.	A weekly paclitaxel regimen was initially considered a relevant comparator for the model, however the available evidence (one abstract) did not provide enough data for the model. Simplifying assumptions had to be made and the possibility of re-challenging with anthracyclines or use of the agents we did consider in different ways, were not included in the model structure. It is the purpose of economic evaluation to bring together data from different sources and to make sense of the available evidence base explicitly using an analytical framework. Whilst inevitably assumptions had to be made, these were made clear to the guideline development group who are charged with interpreting the conclusions of the analysis and using these to make sensible clinical recommendations. These methods are also recommended in the NICE Guidelines Manual.
						Finally, of course, almost all of these datasets are from trials run before the widespread use of taxane-herceptin as first line therapy for HER2 advanced disease, and the modellers appear to have either	It would not be appropriate to take data from one single recent trial reporting better outcomes and ignore data from other trials. Given that the only published evidence from this trial is a meeting

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						ignored this, or assumed that the non-HER2 positive patients will behave just like the HER2 positive ones. One of the few datasets we have from a phase III trial in HER2 negative is the recent AVADO one – and there the single agent docetaxel arm does better in terms of both response rate and TTP than any of the docetaxel monotherapy datasets that they use. Thus we think the whole modelling approach to define an optimum chemotherapy sequence for advanced breast cancer is fundamentally flawed and should not form part of the mainstream guidance.	abstract, it was not possible to incorporate it into the indirect treatment comparison model.
						Decision points – after 1 and 3 cycles – why – toxic death and progression possible after every cycle.	Due to the multitude of treatment options considered in the economic model, we had to keep the model structure simple. The structure we used was adapted from Leung et al and the assumptions were validated by the GDG. We acknowledge that toxic deaths can occur at different points in the treatment course, however since toxic deaths are very rare events this simplification is unlikely to have a big impact on the results of the model. The assumption that patients can only discontinue treatment due to severe toxicity after the third cycle may have more impact on the results. But this was considered the most likely time for the discontinuations to occur by the experts consulted in the Leung paper, and by our guideline development group members.
						Why a time lag of one month between finishing one therapy and starting the next – depends on the circumstances….	We agree it depends on the circumstances– patients could start the next line of treatment sooner or later but the average time lag was considered to be about one month.
						Response can be assessed after 2 or 3 cycles, depending on aggressiveness of disease – but model assumes that if a patient gets to 3 cycles without XS	Yes again we agree. Some patients may go on to receive fewer than six cycles in total, others would receive more than six. However this was felt to be

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						toxicity or progression they will always go on to get 6 – that does not necessarily accord with clinical practise.	a reasonable 'average' estimate.
						Some patients will get more than 3 rounds of chemo – but only a few, and indeed some data suggest that the drop off rate is less if a patient gets more than 3. However these patients are perhaps only 10-20% of all patients so probably don't affect the bulk of the cost – and we don't know if the outcome for these patients, who can be an important tail for survival, could be dependant on the choice of first line therapy.	We assume that you mean 6 rounds of chemotherapy? In the model all patients who responded (complete response, partial response or stable disease) to treatment had six cycles of treatment. Of course in reality patients may receive more than six cycles, but this was also the case in the clinical trials. The mean values derived from the trial evidence therefore include any survival benefit from these additional cycles.
						No consideration is given to the re-challenge with either a taxane or further anthracyclines…	No, this was a simplifying assumption agreed by the GDG and follows other approaches in the economic literature. Furthermore, there is very little data addressing this in the literature, although some studies using taxanes alone or in combination have permitted entry to patients who have previously received adjuvant taxane treatment. The GDG did not feel that including this group in the model warranted the additional complexity that would result.
						The indirect effect of comparing treatments B and C by indirectly comparing A v C and A v B seems to assume that the populations are the same. Surely this is only valid if the populations in the two "A" arms are not only similar, but behave similarly – and this is not always the case.	Yes, the indirect treatment comparison is only valid if we assume consistency between the trial populations. However this assumption is also required to undertake a standard meta-analysis. The indirect comparison crucially assumes that the B (or C) effects would be "similar" in the AvC (or AvB) trials if those treatments had been included as a third arm (i.e. treatment arms missing at random). Note, however, that an economic model based on pairwise comparisons of AvB, AvC and BvC makes the same assumption. Unfortunately, the lack of any "loops" in the evidence structure

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							(Figs 2-3, Appendix 1) means that it is not possible to assess this consistency assumption in this case.
						The model uses overall survival to derive QALY data- yet it admits that there are few RCTs, particularly post first line, and as we all know, OS in phase II studies can vary hugely depending on the patient population included. Thus it seems to us that this part of the analysis is very insecure and it concerns me that the authors come up with such a firm recommendation given the few hard RCT data available to them on which to do the modelling.	Overall survival estimates are required for economic modelling and preparing an economic model was a central requirement for the GDG in this area. The GDG notes with concern the absence of high-quality randomised phase III studies capable of providing the required information for the two agents (vinorelbine and capecitabine), for which this strategy has perforce been adopted. We have made the best use possible of the data available.
						Model assumes that TTP in both responders and non-responders has the same exponential distribution. Is there any evidence to support this…we would have thought that in non-responders there is a bias towards more early progressors, whereas in responders it is shifted to the right, and perhaps may have a different distribution. Few if any studies report TTP curves in primary progressors, so where do they take this assumption from, and how does it influence the conclusion of the model? They take a mean time to progression in progressors as 4.5 weeks…..where does this come from – and then they say that non-assessable patients have the same mean time to progression! They then link time to death in responders and progressors – yet this is surely very risky as rapid progressors may be less likely to get further therapy, whereas responders and slow progressors may still be fit enough to be offered further therapy, which will itself influence survival. They also take a fixed number of months as the time from progression to death – again the same problem exists in that different breast cancers do things at different rates!	The rates for TTP in responders and non-responders are not the same. Non-responders are made up of stable patients, non-assessable patients, and progressive disease patients. A weighted average of the mean TTP across these groups is used to derive the rate for non-responders. Exponential distributions were assumed as a result of limitations in the reported summaries available to us. With only a single summary measure (e.g. median) available it is only possible to fit a distribution with a single parameter (e.g. Exponential). We acknowledge that a Weibull distribution may be more appropriate; however there was no data available on which to estimate the second parameter. The final model that we used was the result of a systematic model fitting process. However, many of the assumptions made were driven by limitations in the data. We have added a section to the Appendix 1 explaining this. The model chosen fitted well to

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							the data. The mean time to progression in progressors is assumed to be equal to 4.5 weeks. This is the mid-point between 0 weeks and 9 weeks when the response assessment is assumed to take place. Due to lack of evidence it was necessary to make an assumption as to TTP rate in non-assessable patients. Non-assessable patients were assumed to be equivalent to progressors. This was considered reasonable since the non-assessable patients are more similar to progressors than responders or patients with stable disease in terms of downstream costs and health outcomes.
						Are there any data at all to support all these assumptions – surely if they are to make national firm recommendations about chemo sequences they have to have robust data to support these assumptions. They then also assume that the impact of second and third line treatments are identical….whilst We understand why, given the lack of hard data, is this valid, and given that there is only one small (EORTC) RCT comparing these two agents in second line, they ignore the low response rates there (9% and 12%) and take almost double those rates (15% and 26%) from phase II studies?? When it comes to costs…. notoriously a minefield and some odd assumptions – it is assumed 50% of neutropenic infections are treated at home (by whom?) and assume all advanced breast cancer patients have access to a CNS and fortnightly visits from a community nurse – This assumption does not match the reality as experienced by our experts!	The EORTC trial was also a phase II study. Given the small number of participants and the high rate of non-evaluable patients, the GDG felt it more appropriate to take data from phase II studies which included larger numbers of patients The cost of treating neutropenic infections was taken from published costs in the literature. In light of your comment we now use a split of 95:5 to estimate the cost of neutropenic infections. This slightly alters the numbers in the base-case scenario, but not the conclusions drawn from the model.
SH	National Cancer Research Institute (NCRI) Clinical	128.4	Full	General		We are very concerned about detailed specific recommendations for the treatment of advanced	We agree that there is no single "right" way to treat advanced breast cancer. This document is a

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	Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians					disease (e.g., patients with HER2+ disease should have anthracyclines first if chemo naïve). There is no single 'right' way to treat advanced breast cancer - this depends on many factors including patient fitness and preference. A fixed algorithm for treatment in a field where management of the disease needs to be tailored to suit the individual is not appropriate.	guideline and not a mandatory approach to clinical practice. As such it does not replace clinical judgement.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.5	Full	General		The organisation of advanced disease management is not addressed. The role of MDT discussion to plan care is not considered other than in the situation of uncontrolled local disease.	This is a clinical guideline and as such the organisation of services is beyond our remit. Service organisation is covered by the NICE Improving Outcomes Guidance on breast cancer (2002).
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.6	Full	General		The provision of specialist nursing support is standard for early disease but not always available for advanced disease patients. The importance of specialist nursing input needs to be stressed.	We agree. We have re-iterated the NICE Improving Outcomes Guidance on breast cancer (2002) with regard to mechanisms to promote continuity of care, in particular provision of a key worker. In many cases this role might be best filled by a specialist nurse.
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of	128.7	Full	General		The important contribution that palliative medicine makes to advanced disease management is not mentioned.	These issues have been covered by previous NICE guidance (Improving supportive and palliative care for adults with cancer, 2004) and are signposted within the recommendations on p73. The GDG felt that it would be duplication to cover them again. In addition the algorithm on p18 includes supportive and palliative care.

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	Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians						
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.8	Full	General		Psychology support not mentioned.	This is mentioned in the recommendations on p73
SH	National Cancer Research Institute (NCRI) Clinical Studies Group and National Cancer Research Network NCRN/ Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.9	Full	General		Major specific comments: 1: Insufficient guidance on the organisation of advanced disease management and composition of advanced breast cancer MDT. 2: Over interpretation of data resulting in a one size fits all sequence of treatments which is not appropriate. 3: Recommendations often more dogmatic than the evidence suggests e.g anti HER2 therapy, radiotherapy to bone etc.	This is a clinical guideline and as such the organisation of services is beyond our remit. Service organisation is covered by the NICE Improving Outcomes Guidance on breast cancer (2002). We agree that there is no single right way to treat breast cancer. This document is a guideline and not a mandatory approach to clinical practice. As such it does not replace clinical judgement. We will respond to specific instances as they are commented on.
SH	National Childbirth Trust	129				This organisation was approached but did not respond.	
SH	National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)	130				This organisation was approached but did not respond.	
SH	National Osteoporosis Society	131				This organisation was approached but did not respond.	

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SH	National Patient Safety Agency (NPSA)	132				This organisation was approached but did not respond.	
SH	National Public Health Service - Wales	133				This organisation was approached but did not respond.	
SH	NCC for Acute Care	134				This organisation was approached but did not respond.	
SH	NCC for Cancer	135				This organisation was approached but did not respond.	
SH	NCC for Chronic Conditions	136				This organisation was approached but did not respond.	
SH	NCC for Mental Health	137				This organisation was approached but did not respond.	
SH	NCC for Nursing & Supportive Care	138				This organisation was approached but did not respond.	
SH	NCC for Primary Care	139				This organisation was approached but did not respond.	
SH	NCC for Women & Children	140				This organisation was approached but did not respond.	
Peer	NCCHTA (1)	141.1	Full	11	18/19	Search strategy doesn't include unpublished literature	This is in accordance with NICE methodology for developing guidelines, which states that NCCs are not routinely expected to search the grey literature.
Peer	NCCHTA (1)	141.10	Full	28	14	Reference to the statement that the outcomes do not appear to vary geographically – does this relate to abc only?	This text refers to advanced breast cancer. The epidemiology of early breast cancer is covered in a separate NICE guideline.
Peer	NCCHTA (1)	141.11	Full	32	6	What type of studies were included in the systematic reviews?	This level of detail is not included in the evidence summaries in the guideline to make them readable. Detail such as this is included in the Evidence Review which accompanies this guideline and is meant to be read alongside it.
Peer	NCCHTA (1)	141.12	Full	32	14	Number retrospective? Also different levels of evidence within the 15 studies – is this taken into account?	This level of detail is not included in the evidence summaries in the guideline to make them readable. Detail such as this is included in the Evidence Review which accompanies this guideline and is meant to be read alongside it.
Peer	NCCHTA (1)	141.13	Full			**Please comment on the health economics and/or statistical issues depending on your area of expertise.**	No response needed

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Peer	NCCHTA (1)	141.14	Full	95 EVIDENCE REVIEW		More information on method of meta-analysis should be provided e.g. based on IPD or aggregate data?	Please see the evidence table (General comments): "Hazard ratios and confidence intervals were constructed at 3 monthly intervals, either with data taken from the published survival curves or obtained indirectly using established methods from available summary statistics". We believe that this indicated the use of aggregate data.
Peer	NCCHTA (1)	141.15	Full	95 (ER)		The number of patients for overall survival analysis =692 but n=817 for tumour response analysis. It is important to describe why the figures differ. I would also be helpful for this and all other analyses throughout to add number of trials included.	6 trials reported 'overall survival' as an outcome and 8 trials reported 'tumour response' hence the patient numbers differ. This level of detail is not included in the evidence summaries in the guideline to make them readable. Detail such as the number of trials is included in the Evidence Review which accompanies this guideline and is meant to be read alongside it.
Peer	NCCHTA (1)	141.16	Full	96 (ER)		There is evidence for statistical heterogeneity between trials for overall survival analysis (p=0.05). This should be discussed and the I2 statistic should be included. Presentation of I2 statistic should be used throughout where possible.	We have amended the evidence table (Results) to include I^2 statistic.
Peer	NCCHTA (1)	141.17	Full	96 (ER)		There is significant (qualitative) heterogeneity in the tumour response analysis hence presenting the overall pooled effect is inappropriate if based on a fixed effects model (which is not clear from the description provided). An explanation for this heterogeneity should be attempted; otherwise a pooled effect (fixed effects) should not be presented. A random effects analysis would incorporate the extra heterogeneity. Also, how do the opposite results relate in terms of survival? Were similar patterns of heterogeneity seen for this outcome too?	These comments relate to the quality of the Cochrane review itself, the authors of which deemed the fixed effect model appropriate for their data. The observed between studies heterogeneity, along with a possible explanation for it, was reported in the evidence table.
Peer	NCCHTA (1)	141.18	Full	98 (ER)		Short summary and full summary on pages 98 and 99 conflict in terms of what is included in this evidence base.	The style used for this Evidence Review is to include all studies in the short summary and then separate the full summary into studies identified in the original search followed by studies identified in the update search. The 2 sections therefore do not conflict.

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Peer	NCCHTA (1)	141.19	Full			Are the studies included in the different reviews and guideline all mutually exclusive?	Despite the high number of studies overall, only one RCT is found in three out of four systematic reviews. Other than that there is minimal overlap between individual reviews.
Peer	NCCHTA (1)	141.2	Full	11	21-23	Is there potential for language bias?	Whilst there is potentially a small risk of bias, we feel this is counteracted by the fact that we do not apply language restrictions to the search and all abstracts are read, so that if a paper of particular importance is identified it can be translated. This is in accordance with NICE methodology for developing guidelines.
Peer	NCCHTA (1)	141.20	Full	99 (ER)		Mauri review – was there evidence of heterogeneity? Table suggests not but text of the summary doesn't highlight this.	We have corrected the evidence summary to include a statement about lack of between studies heterogeneity.
Peer	NCCHTA (1)	141.21	Full	100 (ER)		First paragraph result of HR = 0.88 (95%CI: 0.88-0.96) is quoted – the lower limit of the 95% CI should be below the estimate of HR.	We have made this correction in the Evidence Review.
Peer	NCCHTA (1)	141.22	Full	100 (ER)		First paragraph – need to include result for PFS analysis in text and also the heterogeneity results (p-value and I2 statistic). Again, if heterogeneity present how did the analysis deal with this? If a fixed effects analysis is used to estimate the pooled effect this ignores the statistical heterogeneity. A random effects analysis is usually more appropriate unless an explanation for heterogeneity can be identified (which is preferable). If there is a good deal of heterogeneity the conclusion could change from statistically significant using a fixed effect analysis to non significant using a random effects analysis.	We have amended the evidence summary accordingly.
Peer	NCCHTA (1)	141.23	Full	102 (ER)		The evidence table for the Crump review should include the number of studies. The current data presented suggests that an inappropriate overall combined analysis has been used instead of a meta-analysis.	The number of studies in Crump *et al* (1997) was stated in the evidence table (n=4). The authors describe their analyses in terms of a meta analysis. The level of detail in the evidence review was considered sufficient for the GDG to make their recommendation. This included discussion of the methodology.
Peer	NCCHTA (1)	141.24	Full	105 (ER)		24 degrees of freedom are quoted for the Q statistic but there are only 23 trials (degrees of freedom	The Evidence Review has been corrected

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						should be 22)	
Peer	NCCHTA (1)	141.25	Full	149 (ER)		It is not clear whether the guideline authors intended to undertake a meta-analysis of the identified studies (which would be entirely appropriate and valuable) but didn't have sufficient data to do so (in which case the intended methods of meta-analysis should be described), or whether they did not intend to from the outset and chose to simply summarise the data qualitatively. If the latter, justification should be provided as it is difficult to interpret the evidence in the absence of meta-analysis.	Whilst a meta analysis of data from 5 RCTs would have been feasible it was not possible for this level of work to be undertaken during the limited development time. The level of detail in the evidence review was considered sufficient for the GDG to make their recommendation.
Peer	NCCHTA (1)	141.26	Full	166 (ER)		The comment made that "The advantage was greatest for combinations which did not include their comparator." Can only be made in the context of the comparisons examined and should not be made as a general comment	The Evidence Review has been corrected
Peer	NCCHTA (1)	141.27	Full	167 (ER)		Comment in review: "Looking only at those studies comparing a single agent with a combination therapy which included that agent, the advantage of combined therapy was lower, at 91% (95%CI: 0.85-0.98) (P = 0.02) whilst single agents compared with combination regimes NOT including the single agent were significantly more favourable to the combined therapy, at 83% (95%CI: 0.74-0.92) (P = 0.0003)." These results show that overall combination chemotherapy is superior to single chemotherapy. It also shows that this is still true whether the single arm includes the comparator or not. The CI's for the two subgroups overlap. From a clinical point of view, what is the aim of looking at these subgroups? Should they be expected to be different at all? By virtue of splitting the data into two groups it is likely that one result will be bigger than the other but the overlap in CI's is important.	The decision to undertake separate analyses comparing combination therapies with a single agent that was included, or not, in that combination was made by the authors (Carrick *et al.* 2005) of a high quality Cochrane systematic review. Their conclusions, that combination therapy was superior to single therapy but with more adverse events, was apparently based on this methodology. With reference to overlapping confidence intervals, it was our understanding that point estimates with overlapping confidence intervals may still be statistically significantly different from one another. References: 1] If we're so different, why do we keep overlapping? When 1 plus 1 doesn't make 2. Rory Wolfe and James Hanley. CMAJ January 8, 2002; 166 (1) 2] Overlapping confidence intervals or standard error intervals: What do they mean in terms of

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							statistical significance? Mark E. Payton, Matthew H. Greenstone, and Nathaniel Schenker. J Insect Sci. 2003; 3: 34.
Peer	NCCHTA (1)	141.28	Full	167 (ER)		Single vs combined chemotherapy: why don't the studies included in the carrick review form a subset of the studies in the Takeda review? The review inclusion criteria suggest they should be I think?	Takeda *et al.* (2007) published a review of three unpublished abstracts (as was discussed in the Evidence Review) and hence there was no overlap with Carrick *et al.* (2005).
Peer	NCCHTA (1)	141.29	Full	181 (ER)		Typo for the upper limit of the CI for the HR: "the hazard ratio for OS (0.775 (95%CI: 0.627-9.959 P = 0.018) favours the combined therapy arm."	This typographical error has been corrected in the Evidence Review.
Peer	NCCHTA (1)	141.3	Full	11	41-42	Comment on potential for information specialist to exclude relevant study. A more robust approach would include a second independent person or a random check of a sample of the excluded studies to ensure they should have been excluded.	Whilst a second independent check would be the ideal, this is not possible for every question given the level of resource available. However, for more complex questions information specialists will consult with their colleagues.
Peer	NCCHTA (1)	141.30	Full	185 (ER)		A pooled analysis of single arm trials would provide a valuable summary for the Vinorelbine monotherapy question?	Whilst a pooled analysis of data from phase II studies would have been feasible it was not possible for this level of work to be undertaken during the limited development time. The level of detail in the evidence review was considered sufficient for the GDG to make their recommendation.
Peer	NCCHTA (1)	141.31	Full	187 (ER)		A pooled analysis of the 3 phase II studies assessing VIN+TRZ would provide a valuable summary?	Whilst a pooled analysis of data from phase II studies would have been feasible it was not possible for this level of work to be undertaken during the limited development time. The level of detail in the evidence review was considered sufficient for the GDG to make their recommendation.
Peer	NCCHTA (1)	141.32	Full	227 (ER)		The RCT that compared CAP + DOC with gemcitabine does not appear to fit in with the description of PICO on top of page 228	The inclusion of the Chan *et al.* (2005) RCT was appropriate but the summary had a typographical error. The comparator was gemcitabine plus docetaxel; the detail is apparent elsewhere. This error has been corrected in the review.
Peer	NCCHTA (1)	141.33	Full	228 (ER)		Summary of capecitabine (phase II studies) – a pooled analysis would appropriately incorporate the precision across studies and would provide a	Whilst a pooled analysis of data from phase II studies would have been feasible it was not possible for this level of work to be undertaken

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						valuable summary estimate.	during the limited development time. The level of detail in the evidence review was considered sufficient for the GDG to make their recommendation.
Peer	NCCHTA (1)	141.34	Full	270-271 (ER)		Meta-analysis would be appropriate to provide an overall summary of the evidence, increase statistical power and also provide a summary of how the individual trial results may differ.	Whilst a pooled analysis of data from phase II studies would have been feasible it was not possible for this level of work to be undertaken during the limited development time. The level of detail in the evidence review was considered sufficient for the GDG to make their recommendation.
Peer	NCCHTA (1)	141.35	Full	271		I do not agree with the comment made that "Using a random-effects model does not adjust for these differences which must therefore be borne in mind when considering the apparent significance of results". A random effects model does take into account the statistical heterogeneity between trials and increases the width of the confidence interval for the pooled effect. A random effects model does not explain the cause of the heterogeneity but does adjust for it	This paragraph has been rewritten.
Peer	NCCHTA (1)	141.36	Full	272		First two paragraphs (TTP/response results) – is the quoted result derived from a random effects model? It is very important to state which model was used for analysis	The data in Ghersi *et al.* (2005) were analysed using a fixed effects model. The authors made a lengthy explanation in response to the high levels of between study heterogeneity, particularly for the outcomes of tumour response and time to progression. An appropriate amendment has been made to the Evidence Review.
Peer	NCCHTA (1)	141.37	Full	272		Under the description for Bria study, a comment is made that "However, tumour response was significantly different between arms in favour of taxane-containing therapies (P <0.001) by either method of data analysis (using median time to event data or log of relative risk)…." Tumour response is not a time-to-event endpoint so it is not possible to summarise as median time to event data (unless the authors examined time to achieve a tumour response or some other measure which should be described in more detail if this is the case).	Tumour response was analysed in two ways by Bria *et al*. Method A involved calculating the log of relative risk given by the ratio between rates in the two study arms and applying this to a fixed effect model using weights based on sample size. For Method B the log of relative risk was estimated and applied to fixed (inverse variance) and random effect (Mantel-Haentzel) models. The evidence review has been amended to make this clear.

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Peer	NCCHTA (1)	141.38	Full	Health economics		No comments – methodology looks very rigorous. Similar methodology would be appropriate to provide an overall clinical summary of the evidence (mixed treatment comparisons)	Thank you.
Peer	NCCHTA (1)	141.39	Full	Ongoing management of advanced breast cancer patients in the community setting		I would question the clinical relevance of the studies that include patients with other cancer types. e.g. multiple myeloma and head and neck cancer. I would suggest only studies including metastatic breast cancer patients should be included which reflects the rest of the guideline. There are likely to be important differences in patients with different cancer types that could impact on the relative treatment differences.	Due to the lack of literature specifically concerning breast cancer, the GDG requested the topic be re-examined for all advanced cancer patients.
Peer	NCCHTA (1)	141.4	Full	12	19	Only one researcher undertook critical appraisal and data extraction – this should also be done by two independent reviewers to be more robust.	Whilst we agree that this would be the ideal this is not possible for every question given the level of resource available.
Peer	NCCHTA (1)	141.40	Full	6.1 Management of lymphoedema		The defined population of 'Patients with lymphoedema who have completed their primary cancer treatment and have no active disease' relates to early breast cancer patients. This is not the population of interest in this current guideline? It appears the population has been defined to fit in with the evidence rather than defining the population of interest and identifying a lack of evidence relevant to that population. It may be appropriate to make a cross-reference to the early breast cancer guideline in the absence of evidence for metastatic patients but I do not think it is appropriate to include the evidence in the current guideline and define the population in this way.	The PICO was set by the GDG after extensive discussions. The treatment for lymphoedema is considered appropriate for women with advanced and/or metastatic breast cancer
Peer	NCCHTA (1)	141.41	Full	398 (ER)		Evidence table – number of trials in the minton review not quoted	4 papers were relevant to the PICO – this is stated in the evidence review.
Peer	NCCHTA (1)	141.42	Full	General comment		A number of meta-analysis results have been presented based on a fixed effects model in the presence of significant statistical heterogeneity. However, a fixed effects model assumes that each study is estimating the same underlying effect and	Where applicable, these details have been amended in the evidence review. However, these points would have been discussed when presenting the evidence at GDG meetings.

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						does not make any allowance for statistical heterogeneity. An explanation for heterogeneity should be identified and a random effects model considered which makes allowance for the heterogeneity and results in a less optimistic conclusion.	
Peer	NCCHTA (1)	141.43	Full	35	2-4	**How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? B) Complete? i.e. are all the important aspects of the evidence reflected?**	No response needed
Peer	NCCHTA (1)	141.44	Full	35	2-4	There is no evidence that PET /CT improves management – this can only reliably be explored in a properly randomised study. The recommendations are overstated given the evidence.	The recommendation is that PET-CT is not used for monitoring disease progression which is entirely consistent with the evidence.
Peer	NCCHTA (1)	141.45	Full			**Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**	No response needed
Peer	NCCHTA (1)	141.46	Full	General comment		Reports are well written. However the evidence review document is very hard to interpret. When several reviews and RCTs are available addressing the same question, it would facilitate decision making to present combined analyses where appropriate. Is there a reason why this has not been done? This would be particularly helpful to put the 'new' evidence into context and would also provide a bigger data set to investigate heterogeneity of treatment effects. Given the number of treatments of interest, a mixed treatment comparison analysis would be extremely valuable here and would make interpretation of results much easier.	There were insufficient resources to allow such detailed statistical analyses to be undertaken during the limited development time.
Peer	NCCHTA (1)	141.47	Full	General comment		Forrest plots and I2 statistics should be presented for all meta-analyses. Particularly in the absence of forrest plots (which would aid interpretation).	Copying Forest plots or other diagrams from publications is considered plagiarism and therefore we do not reproduce these in our guideline. The I^2 statistic is reported in evidence tables where appropriate.

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Peer	NCCHTA (1)	141.48	Full	General comment		Methods of meta-analysis need to be described in more detail in both the evidence review document but particularly the full guideline.	Where applicable, these details have been amended in the evidence review.
Peer	NCCHTA (1)	141.5	Full	12	22	Table A referred to as SIGN checklist but I do not believe this is the SIGN checklist?	We have amended the text to clarify.
Peer	NCCHTA (1)	141.6	Full	12	24/25	There is a SIGN checklist for diagnostic studies (QADAS tool)	Thank you for this comment. We are aware of the existence of the QADAS tool.
Peer	NCCHTA (1)	141.7	Full	18		Overview of pathway – not clear what the two large arrows are pointing towards. Also, managing complications of disease + supportive/palliative care are options available alongside sequential systemic therapy decision but this is not clear from the pathway presented.	The arrows are intended to convey that managing complications and supportive and palliative care should happen throughout the pathway – they do not point to anything. We have removed the arrows that point to these components to aid clarity
Peer	NCCHTA (1)	141.8	Full	19		Under diagnosing advanced breast cancer imaging assessment – imaging equivocal but high suspicion of mets – replace 'but' with 'or'. For the final decision – where does diagnosis of abc confirmed but extent of mets not known fit in?	This change is not appropriate as it would change the meaning of the algorithm. The text "extent of metastases known" has been removed from the algorithm.
Peer	NCCHTA (1)	141.9	Full	21		"other chemotherapy" – which ones?	We assume you are talking about the box that says "offer chemotherapy". Patients reaching this box should go to the chemotherapy algorithm (p22) to determine what agents they receive.
Peer	NCCHTA (2)	141.49	Full			**1.1 Are there any important ways in which the work has not fulfilled the declared intentions of the NICE guideline (compared to its scope – attached)**	No response needed
Peer	NCCHTA (2)	141.50	Full			The intentions appear to be fulfilled	Thank you
Peer	NCCHTA (2)	141.51	Full			**2.1 Please comment on the validity of the work i.e. the quality of the methods and their application (the methods should comply with NICE's Guidelines Manual available at http://www.nice.org.uk/page.aspx?o=guidelinesmanual).**	No response needed
Peer	NCCHTA (2)	141.52	Full			The methods are explained thoroughly but some questions remain	Thank you
Peer	NCCHTA (2)	141.53	Full	11	21	We are told that reviews are restricted to SRs and RCTs when necessary. What criteria define	We have amended the text to clarify.

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						necessity? It would perhaps be more natural to say they were extended beyond these where necessary as the number of RCTs or SRs was too small.	
Peer	NCCHTA (2)	141.54	Full	12	38-46	I appreciate that these are the NICE guidelines but nothing has been said about how, for example, the evidence from a case-control study is classed as having a high probability of causality. Most case-control studies, by the nature of their design, cannot give causal proof and so criteria would be helpful.	This table and the information contained within it are taken directly from the NICE Guidelines Manual 2007. We are therefore unable to change it.
Peer	NCCHTA (2)	141.55	Full			Data extraction is often extremely difficult as authors sometimes seem to go to great lengths to obscure their results. However the data extracted could sometimes have been presented more clearly to aid interpretation, and there could have been a stronger critical assessment of the results.	Thank you for these observations
Peer	NCCHTA (2)	141.56	Full	32		To illustrate this consider the evidence on imaging for diagnosis. In the evidence review a table is presented on p5 showing sensitivity and specificity from a range of studies. Numbers of participants are shown but are not broken down into those with the condition being sought and those without. This is important as these numbers are required for estimating sensitivity and specificity.	The table was intended as a quick reference only, showing study name, principal outcomes etc. The number of patients was included only to indicate the size of the study in question.
Peer	NCCHTA (2)	141.57	Full	32		If we look at one of the studies, say Eubank (2001), we are told on p21 that the outcome was to compare the prevalence of suspected disease based on abnormal findings with FDG-PET versus CT.	Thank you for these observations
Peer	NCCHTA (2)	141.58	Full	32		Many questions arise from this. As FDG-PET and CT are the technologies whose sensitivities and specificities are being compared, this back-to-front.	Thank you for these observations
Peer	NCCHTA (2)	141.59	Full	32		The sensitivity would be the proportion of true cases of disease identified by, say, FDG-PET but the wording suggests they have calculated the predictive value, the proportion of cases of disease in those positive by FDG-PET.	The authors were interested to calculate the predictive properties of these imaging methods but, as a by-product of their study, also calculated the sensitivity and specificity based on data from those women for whom these preliminary imaging results were later confirmed to have a presence or absence of disease.
Peer	NCCHTA (2)	141.60	Full	32		The summary goes on to say that only 40 of the 73	Of 73 women, 33 had their nodal status (presence

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						were verified as regards disease status (7 of which seem to have been confirmed by the technology being tested!?)	or absence) confirmed at a later date by various means including clinical follow-up and histology (also CT). The raw data for these patients were not given but the sensitivity and specificity results from the authors' own analysis was presented and was reproduced in the evidence review. It seemed not inappropriate that follow-up CT was used to asses the accuracy of these imaging modalities since there was no other way that this could be achieved in the absence of more invasive techniques i.e. surgery etc.
Peer	NCCHTA (2)	141.61	Full	32		The confidence intervals for sensitivity and specificity seem to be based on these 40. However the sensitivity is calculated from the number who were truly positive and the specificity from the number who were truly negative and there is no mention of the denominators (and both cannot be 40 as there were only 73 in total and 33 appear not to have had the diagnosis checked)	As stated above, the data relevant to the accuracy outcomes were not shown. This was not the author's intention in conducting this retrospective review.
Peer	NCCHTA (2)	141.62	Full	32		So at best the summary is very confusing and I may have misinterpreted it. This may be the fault of the paper or the way in which data have been extracted. If the former is the case then there should have been very critical comments. On reading the paper it seems that both explanations are correct. The results in the paper, given the data contained there, are incorrect and the interpretation of them in the summary is misleading.	The paper gave a great deal of detail about the outcomes in which they were interested including complex statistical analyses. The accuracy data were abstracted from this paper and was assumed to be correct and were reported as shown.
Peer	NCCHTA (2)	141.63	Full	32		I do not want to over-emphasise this example, but the summary in the text on page 5 says this study showed that FDG-PET was superior to CT. To reach such a conclusion we would need to be reassured that the sensitivity and specificity had been properly calculated, and appropriate methods used to derive confidence intervals, and that is far from clear. The analysis would also be a paired-analysis, since the methods were compared with a gold standard on the	The paper gave a great deal of detail about the outcomes in which they were interested including complex statistical analyses. The accuracy data were abstracted from this paper and was assumed to be correct and were reported as shown.

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						same subjects, and there is no mention of this.	
Peer	NCCHTA (2)	141.64	Full	32		Incidentally the summary of the results following the table on p3-6 of the evidence review is not correct.	This oversight (the addition of studies after this summary had been written) has been corrected appropriately.
Peer	NCCHTA (2)	141.65	Full	32		This is just an example and the main recommendations based evidence are derived from systematic reviews, where the detail in individual papers is likely to have been sorted by the authors of the review, and so it is unlikely to affect the major findings. However it is a matter of concern.	Thank you for these observations
Peer	NCCHTA (2)	141.66	Full			**2.2 Please comment on the health economics and/or statistical issues depending on your area of expertise.**	No response needed
Peer	NCCHTA (2)	141.67	Full	Many		There is too much emphasis generally on summarising studies by whether the results were statistically different or not. While this matters, at least as important is to quote results on effect size, such as hazard ratios or median survival times.	There were several pieces of evidence presented to the GDG that informed their recommendations, including details of effect size, confidence intervals, heterogeneity etc. This level of detail is not included in the evidence summaries in the guideline to make them readable. Detail such as this is included in the Evidence Review which accompanies this guideline and is meant to be read alongside it.
Peer	NCCHTA (2)	141.68	Full	Many		This is especially true for small studies which have relatively low power and so the reporting of a non-significant result is unremarkable. A non-significant result could be consistent with an important difference in such a study and that is not shown.	There were several pieces of evidence presented to the GDG that informed their recommendations, including details of effect size, confidence intervals, heterogeneity etc. This level of detail is not included in the evidence summaries in the guideline to make them readable. Detail such as this is included in the Evidence Review which accompanies this guideline and is meant to be read alongside it.
Peer	NCCHTA (2)	141.69	Full	Many		Admittedly such studies are unlikely to be crucial in producing recommendations but in those which do show a significant difference the emphasis is still on the P-values rather than the effect size.	There were several pieces of evidence presented to the GDG that informed their recommendations, including details of effect size, confidence intervals, heterogeneity etc. This level of detail is not included in the evidence summaries in the guideline to make them readable. Detail such as

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							this is included in the Evidence Review which accompanies this guideline and is meant to be read alongside it.
Peer	NCCHTA (2)	141.70	Full	Many		In the end what matters is possible benefit to patients. So a hazard rate of 0.7 is much better than one of 0.9 when comparing 2 treatments and reporting this is more important than saying a P-value is 0.001,	There were several pieces of evidence presented to the GDG that informed their recommendations, including details of effect size, confidence intervals, heterogeneity etc. This level of detail is not included in the evidence summaries in the guideline to make them readable. Detail such as this is included in the Evidence Review which accompanies this guideline and is meant to be read alongside it.
Peer	NCCHTA (2)	141.71	Full	53	48	To illustrate this take the study of Pajk, reported as underpowered. The overall response rates were 2/23 compared with 3/24, not significantly different. However a 95% confidence interval for the difference is (-23%, 16%) and so the results could be consistent with possibly large differences.	This paper reported a very underpowered study in which even the authors admitted a comparison between treatment arms was of no value since a significant difference between them would not have been detected. Hence the large confidence interval has no more evidential meaning than the data. This was reported as a study of little value in the evidence review.
Peer	NCCHTA (2)	141.72	Full	51	42	This describes a large review showing a benefit for survival. But the benefit is not quantified here and we have to turn to the large evidence review and search for it. The fact it is a hazard ratio of 0.88 (0.83, 0.94) is relevant to the recommendation	There were several pieces of evidence presented to the GDG that informed their recommendations, including details of effect size, confidence intervals, heterogeneity etc. This level of detail is not included in the evidence summaries in the guideline to make them readable. Detail such as this is included in the Evidence Review which accompanies this guideline and is meant to be read alongside it.
Peer	NCCHTA (2)	141.73	Full			I am a statistician rather than a health economist and there is very little explicit reference to statistics. However Appendix 1 contains a very detailed economic model with considerable statistical components.	Thank you
Peer	NCCHTA (2)	141.74	Full			The model is described in much detail, and looks plausible (though some terms in the model equations are not defined or explained)	We agree the model equations may not be clear so a key to explain and facilitate the reader's understanding has been added.
Peer	NCCHTA (2)	141.75	Full			There are many assumptions made with no comment about the basis for them. For example it is assumed	Exponential distributions were assumed as a result of limitations in the reported summaries available to

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						that times to progression or death follow exponential distributions. Is there evidence for that? That implies a constant hazard function, which does not seem particularly plausible, but there may be evidence for it. Is it crucial? Would it be much more complex to assume, for example, a Weibull distribution. This is much more general and contains the exponential as a special case.	us. With only a single summary measure (e.g. median) available it is only possible to fit a distribution with a single parameter (e.g. Exponential). We acknowledge that a Weibull distribution may be more appropriate; however there was no data available on which to estimate the second parameter. The final model that we used was the result of a systematic model fitting process. However, many of the assumptions made were driven by limitations in the data. We have added a section to Appendix 1 explaining this. The model chosen fitted well to the data.
Peer	NCCHTA (2)	141.76	Full			The summaries of the papers by Martin and Pierga, whose results are cited in several tables, only contain results on the median survival times. If means and SDs were given then there would be some justification for the assumption. But perhaps these are not shown in the papers.	The Martin and Pierga papers do not report mean survival times. As such we were forced to assume an exponential distribution to calculate the mean values from the median survival times reported in the papers.
Peer	NCCHTA (2)	141.77	Full			The model is complex but there is little evidence shown here about its validation. `	More detail has been added to the final report to address these concerns.
Peer	NCCHTA (2)	141.78	Full	General		**3.1 How far are the recommendations based on the findings? Are they a) justified i.e. not overstated or understated given the evidence? b) Complete? i.e. are all the important aspects of the evidence reflected?**	No response needed
Peer	NCCHTA (2)	141.79	Full	General		The basis of the recommendations is made clear.	Thank you
Peer	NCCHTA (2)	141.80	Full	General		More often than one would like it is based on consensus opinion of the GDG.	Stakeholders had input into which topics the guideline investigated. Where the evidence was limited, GDG consensus was used to create recommendations in accordance with NICE methodology. This document is a guideline and not a mandatory approach to clinical practice. As such it does not replace clinical judgement.
Peer	NCCHTA (2)	141.81	Full	General		Sometimes when an evidence source is quoted the reference is not very precise. For example we may be told '.. recommendations are based on limited trial evidence..' but it may not be easy to immediately	The relevant evidence is contained in the "Evidence Summary" sections that follow immediately after the recommendations. We feel that this is an appropriate and understandable way

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						identify the evidence to which they are referring and references could have been given there, rather than being a bit hidden in the later text.	to display this information.
Peer	NCCHTA (2)	141.82	Full	General		**3.2 Are any important limitations of the evidence clearly described and discussed?**	No response needed
Peer	NCCHTA (2)	141.83	Full	General		As indicated above in many cases it is noted that the quality or quantity of the evidence is insufficient to make an evidence-based recommendation and that instead expert opinion has been used. There is often an accompanying research recommendation to provide evidence to resolve the issue.	Thank you
Peer	NCCHTA (2)	141.84	Full			As noted in 2.1 there are cases where the evidence in the summary of a paper is unclear. I included just one illustration there but there are others when the either the summary is misleading or the study has been given sufficient critical comment.	We have noted your comments
Peer	NCCHTA (2)	141.85	Full	General		**4.1 Is the whole report readable and well presented? Please comment on the overall style and whether, for example, it is easy to understand how the recommendations have been reached from the evidence.**	No response needed
Peer	NCCHTA (2)	141.86	Full	General		The report is generally well presented. Some parts are easy to read but others, particularly some of the sections on chemotherapy, are less clear, in the sense that the overall conclusions for a particular drug or drugs are not summarized very clearly.	We will review these sections and make changes where we feel they are needed
Peer	NCCHTA (2)	141.87	Full	7	12-13	As in any long document there are instances where wording is unclear and these will probably be resolved at the next stage of editing. The example cited here is minor, and that reflects the accuracy of the vast majority of the text.	Thank you. We have amended the text to clarify.
Peer	NCCHTA (2)	141.88	Full	General		**4.2 Please comment on whether the research recommendations, if included, are clear and justified.**	No response needed
Peer	NCCHTA (2)	141.89	Full	General		As far as I could tell they were justified and they were certainly clear. They seem to have identified the most important issues (with my background I cannot confirm their selection) where evidence is lacking and	Thank you

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						have made suggestions in those areas.	
Peer	NCCHTA (2)	141.90	Full	General		As so many issues lack definitive evidence, establishing priorities is important.	Thank you – we agree
Peer	NCCHTA (2)	141.91	Full			**Please make any additional comments you want the NICE Guideline Development Group to see, feel free to use as much or as little space as you wish.**	No response needed
Peer	NCCHTA (2)	141.92	Full	12	18-20	Time has not permitted a review of all the evidence in the evidence review. I have illustrated some of the difficulties with the example above in 2.1 but there are others. I noted that a single reviewer extracted the data from each paper. In my experience of performing systematic reviews, it is normal practice for two reviewers to extract data independently, or at the very least for the data extracted by one to be checked by another, and I am surprised that this was not done.	Whilst we agree that this would be the ideal this is not possible for every question given the level of resource available.
SH	Newcastle PCT	142				This organisation was approached but did not respond.	
SH	Newham Primary Care Trust	143				This organisation was approached but did not respond.	
SH	NHS Bedfordshire	144				This organisation was approached but did not respond.	
SH	NHS Cancer Screening Programme	145				This organisation was approached but did not respond.	
SH	NHS Clinical Knowledge Summaries Service (SCHIN)	146				This organisation was approached but did not respond.	
SH	NHS Direct	147	Full	General		NHS Direct has considered the draft document. No comments	Thank you
SH	NHS Kirklees	148				This organisation was approached but did not respond.	
SH	NHS Plus	149				This organisation was approached but did not respond.	
SH	NHS Purchasing & Supply Agency	150				This organisation was approached but did not respond.	
SH	NHS Quality Improvement Scotland	151				This organisation was approached but did not	

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						respond.	
SH	Norfolk Suffolk and Cambridgeshire Local Specialised Commissioning Group	152				This organisation was approached but did not respond.	
SH	North East London Cancer Network	153				This organisation was approached but did not respond.	
SH	North East London Strategic Health Authority	154				This organisation was approached but did not respond.	
SH	North Eastern Derbyshire PCT	155				This organisation was approached but did not respond.	
SH	North Lincolnshire Primay Care Trust	156				This organisation was approached but did not respond.	
SH	North Tees PCT	157				This organisation was approached but did not respond.	
SH	North Yorkshire and York PCT	158				This organisation was approached but did not respond.	
SH	Nottingham City Hospital	159				This organisation was approached but did not respond.	
SH	Nottingham University Hospitals NHS Trust	160				This organisation was approached but did not respond.	
SH	Novartis Pharmaceuticals UK Ltd	161.0	General			The guideline development group should include representation from a clinical oncologist perspective. It is important that the views of this group of clinicians are taken into account in order to improve the quality of the guideline and ultimately the quality of care for breast cancer patients.	The GDG included representation from 2 clinical oncologists (see Appendix 6.1 of the full version)
SH	Novartis Pharmaceuticals UK Ltd	161.1	Full version	80	37-39	The Guidelines state "Although bisphosphonates are frequently used, it is not clear whether oral or intravenous therapy is better or which bisphosphonate is the most effective". In light of the evidence supplied below from randomised controlled trials (RCTs), meta-analyses, and clinical guidelines in the use of bisphosphonates in metastatic breast cancer we believe it is possible to demonstrate superiority in terms of intravenous (IV) bisphosphonates over oral, and nitrogen containing	As we state in our qualifying statement for the recommendation on p81 (line 2-4), there was no strong evidence of comparative clinical effectiveness for any of the bisphosphonates. In addition there was conflicting health economic evidence over which bisphosphonate was the most cost-effective, although as a class of drugs they do seem to be cost-effective. The GDG therefore felt that it was not possible to recommend a specific bisphosphonate.

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						bisphosphonates over non-nitrogen containing bisphosphonates. In addition, there is evidence to suggest that zoledronic acid is superior to the other bisphosphonates in this setting. Zoledronate (Zometa) and pamidronate are the only bisphosphonates to have demonstrated statistically significant benefits across multiple end points and as such should be considered the standard of care for advanced breast cancer with bone metastases. The ASCO 2003 "Guidelines for Breast Cancer Patients with Bone Health Issues on Bisphosphonates" only discuss the use of iv pamidronate and zoledronate as treatment options. It is also important to note that clodronate and ibandronate failed to gain licences in the US in this setting. Advanced breast cancer with bone metastases is associated with a very high risk of skeletal events with often painful and debilitating consequences. This results in poor outcomes for patients. Results from placebo controlled trials demonstrate that nearly 70% of patients not receiving a bisphosphonate will experience 1 or more SREs, and around 50% will have a pathological fracture within 2 years (Hortobadgyi 1998). Importantly experiencing a pathological fracture increases the risk of death in breast cancer patients by 32% (Hei et al 2005). It is therefore important to ensure that patients are protected from these events and the associated complications. In addition to the patient benefits conferred by bisphosphonates, the substantial costs of treating complications can be reduced. It is therefore important that these guidelines recommend the most clinically and cost-effective bisphosphonates based on the available evidence. <u>IV bisphosphonates are superior to oral</u>	Rosen et al. 2004 is retrospective sub-group analysis of data from Rosen et al. 2001. Rosen et al. 2001 was an equivalence study of 1500 patients. It only recruited 1100 patients so was underpowered and was only designed to show equivalence of the interventions. Therefore the GDG do not feel that this trial can be used as the basis for changing the recommendation as you suggest.

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						bisphosphonates: Published data suggest that IV bisphosphonates are superior to oral bisphosphonates. Oral bisphosphonates are associated with inconvenient and complex dosing schedules, which increase the risk of adverse effects, especially when dosing recommendations are not adhered to. In addition the very low absorption rates of oral bisphosphonates even under ideal conditions may contribute to poor outcomes Emkey et al 2006. According to Conte et al 2004, the poor bioavailability of of oral bisphosphonates (generally <5% even when dosing regimens are adhered to), and the high oral dose that must be administered to achieve therapeutic effect, leads to poor tolerability and compliance in an oncology setting. This remains a problem despite attempts to educate patients on the importance of keeping to the specified dosing schedules. Data from clodronate trials demonstrated that compliance for those on treatment for longer than six months was at 74% for complete or partial compliance, and 26% total non-compliance (Paterson et al 1993). In addition 16% on clodronate and 18% on placebo reported difficulty in swallowing the tablets because of their size (Robertson et al 1995). It is also likely that compliance within the framework of a clinical trial will be better than compliance in a real life setting. The IV bisphosphonates which are administered on a monthly basis are likely to have less compliance issues than the oral formulations. In the trial referred to above involving 173 metastatic breast cancer patients on clodronate, 34% of the patients discontinued the study drug, including 22% of patients who withdrew because of early non-	

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						compliance (< 6 weeks) Paterson et al 1993. There are several other studies showing similar or larger rates of non-compliance for oral therapies. Early and durable reductions in adherence are often associated with adverse events. This is not just an effect associated with first generation clodronate, but also with second generation oral ibandronate (2^{nd} generation meaning the nitrogen containing bisphosphonates). A high rate of early GI withdrawal due to GI adverse events was reported in the study by Coleman et al 1999. This was a dose-finding study where patients received doses from 5-50mg/day [50 mg/day is the approved licensed dose]; 8% of patients discontinued within 1 month because of GI intolerability. Summarily in the pooled analysis of oral ibandronate (Body et al 2004) 26% of patients receiving oral ibandronate on the study had a drug related AE, compared to 17.7% in the placebo group. The complexity of the dosing regimens to maintain efficacy often include periods of fasting prior to, and immediately after dosing. In addition patients must not ingest food or drink (including bottled water) and must remain upright for some time after administration in order not to adversely affect absorption, bioavailability and ultimately efficacy. In the case of oral ibandronate, tablets should be taken after an over night fast (at least 6 hours) and before the first food or drink of the day. Medicinal products and supplements (including calcium) should summarily be avoided prior to taking Bondronat. As these patients may be on several other therapies this could potentially be very problematic. Patients can only ingest plain water within 30 minutes post-dosing and should not lie down within 1 hour after administration. A study of ibandronate in PMO	

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						investigated the effects of a 30-minute versus 60-minute post-dose fasting period (Tanko et al 2003). The study demonstrated an approximate 50% reduction in efficacy when patients ate within 30 minutes of administration based on measurements of bone mineral density (an accepted surrogate marker for bisphosphonate efficacy). However in the group that fasted for 60 minutes post-dosing there was a higher incidence of GI side effects. Meaning that neither situation is ideal and there is a very delicate balance which is easily altered. Although health economic studies evaluating the impact of non-compliance of oral therapies are limited, the available evidence suggests that non-compliance can result in increased morbidity and burden of disease which increases health care costs. The increased health care costs stem from more frequent physician visits, diagnostic testing, hospital admissions, and longer hospital stays for patients who do not comply with the treatment regimen. These economic factors should be taken into consideration when deciding which bisphosphonate should be recommended. Data gathered from insurance claims databases of metastatic disease patients (breast and other solid tumours) confirms that the data gathered for compliance in PMO oral bisphosphonate use is also at least as likely to be reflected in the metastatic setting. Data shows that at 3 months, 44% of patients had stopped taking medication and at 6 months 65% had stopped taking medication (Heatley et al 2006). The Aapro et al 2007 clinical guideline, "Guidance on the use of bisphosphonates in solid tumours; recommendations of an international expert panel" was written by an interdisciplinary expert panel of	

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						clinical oncologists and of specialists in metabolic bone disease. The panel assessed the widespread evidence and information on the efficacy of bisphosphonates in the metastatic and non-metastatic setting; authors of this paper included all the primary authors of the key papers associated with the registration trials for all the licensed bisphosphonates in the metastatic setting. The conclusion of the review in terms of oral versus iv was, "… iv administration is most often preferable, oral administration (clodronate, ibandronate) may be considered for breast cancer patients who cannot or do not need to attend regular hospital care". It was also noted that oral administration requires precautionary measures to ensure absorption and for some bisphosphonates to avoid gastrointestinal adverse events. In summary we believe that the NICE Breast Cancer Guideline (Advanced) should be consistent with the data and Aapro Guideline presented above by recommending iv bisphosphonates over oral bisphophonates to ensure compliance and maximum efficacy. Oral bisphosphonates should be reserved for those patients who cannot or do not need to attend regular hospital care. <u>Nitrogen bisphosphonates are preferable to non-nitrogen containing bisphosphonates:</u> In order to be consistent with the Aapro Guideline 2007, amino-bisphosphonates, commonly referred to as nitrogen containing bisphosphonates should be recommended over non-nitrogen containing bisphosphonates. It is well accepted that the newer nitrogen containing bisphosphonates pamidronate, ibandronate, and	

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						zoledronate are several orders of magnitude more potent than first generation non-nitrogen containing bisphosphonates. Green at al 2004 demonstrated that . clodronate is less potent than pamidronate which in turn is less potent that zoledronate. The variability in structure and potency has substantial biological and clinical implications. This increase in potency means that the drug can be given in much smaller doses whilst remaining clinically effective. This reduction in dose means the drug can be infused over a shorter timeframe and the lower dose means a reduced risk of adverse events. Administration of pamidronate 90mg requires an infusion over 90-270 minutes, ibandronate 6mg (reduced to 2mg for severe renal impairment) requires an infusion over 15-60 minutes and zoledronate 4mg requires an infusion over 15 minutes. The infusion time will also have resource and cost implications both for infusion clinics and infusions in the community. A study by Joshua et al in 2002 demonstrated that zoledronate reduced clinic times by 50% when compared to pamidronate, 78 minutes for zoledronate vs. 161 minutes for pamidronate; p=<0.001. In patients who did not require concomitant procedures the difference in mean treatment times in beds or chairs was even greater, 59 minutes for zoledronate vs. 161 minutes for pamidronate p= <0.001. These data suggest that infusion clinics could increase capacity to treat patients with bisphosphonate infusions by 107% by using zoledronate. The data of Chern et al 2004, also suggests that patients prefer the shorter infusion time. In the study by Chern et al, n= 138, 92% preferred zoledronate to pamidronate because the shorter infusions caused	

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						less disruption to their day. Therefore infusion time is an important consideration when choosing which nitrogen containing bisphosphonates,to offer a patient. In summary the above data suggest that nitrogen containing bisphosphonates confer practical advantages over non-nitrogen containing bisphosphonates with respect to the required infusion time and impact on associated costs and resource needs. The recommendations should take these advantages into account. <u>Zoledronate is the most efficacious bisphosphonate:</u> RCT evidence: Rosen et al 2003: This is the only appropriately powered phase III, head to head study comparing zoledronate and pamidronate and although this was designed as a non-inferiority trial there was a statistically significant advantage in favour of zoledronate. In the overall study there was equivalent efficacy for the two bisphosphonates with regard to the risk of developing skeletal related events (SREs), skeletal morbidity rate (events per year), and the time to skeletal event, pain and quality of life. However this trial involved patients with both multiple myeloma and breast carcinoma. Post-hoc sub-group analysis of the breast carcinoma patients and specific groups within this population also showed a significant difference in favour of zoledronate. Zoledronate reduced the skeletal morbidity rate by 40% although this was not statistically significant (0.9 vs. 1.49 events per year, P = 0.125). This difference was even greater when hypercalcaemia of malignancy (HCM) was added although this also did not reach significance. However by the more statistically robust multiple	

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						event analysis using Anderson-Gill method (Cook et al 2001) 4mg zoledronate every 3-4 weeks reduced the overall risk of developing skeletal complications by 20% compared to pamidronate 90mg every 3-4 weeks (relative risk (RR) = 0.799; P= 0.025). Meta-analyses: It has also been demonstrated from data gathered in a meta-analysis by the Cochrane Collaboration Pavlakis et al 2005 "Bisphosphonates for Breast Cancer (review)" that of all bisphosphonates, when compared against placebo zoledronate shows the greatest reduction in overall risk of skeletal events in advanced breast cancer, by individual drug at the recommended dosing (Analysis 1.4). It also states in the 'main results' section that benefit was most certain with iv zoledronate, iv pamidronate, and oral clodronate. Guidelines: There are several clinical guidelines for the use of bisphosphonates in metatstatic breast cancer; the most recent one by Aapro et al 2007 "Guidance on the use of bisphosphonates in solid tumours: recommendations of an international expert panel". This guideline is based on the available evidence base including the Pavlakis et al 2005 Cochrane Review and recommends a nitrogen containing bisphosphonate. The Aapro review used overall risk reduction for skeletal events to demonstrate the efficacy of bisphosphonates in breast cancer, where the greatest benefit was demonstrated for zoledronate. In conclusion, the available clinical evidence, current clinical guidelines and a meta-analysis consistently recommend zoledronate and pamidronate over and above the other bisphosphonates. In addition	

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						zoledronate confers an additional benefit in that it requires a significantly shorter infusion time than pamidronate.	
SH	Novartis Pharmaceuticals UK Ltd	161.2	Full version	80	44-45	The draft guideline states, "Offer bisphosphonates to patients with newly diagnosed bone metastases, to prevent skeletal related events and to reduce pain." In order to be consistent with the available evidence base (described in detail above) and other evidence based clinical guidelines the above recommendation should be amended as follows, "Offer zoledronate and pamidronate to patients with newly diagnosed bone metastases, to prevent skeletal related events and to reduce pain." It should be noted that zoledronate and pamidronate are the only two bisphosphonates to show clinically and statistically significant results across multiple end points Therefore the results of the Cochrane review by Pavlakis et al 2005, and the results of the Rosen et al 2003 paper should be included in the evidence section of the guideline in order that the clinical data are comprehensively, accurately and appropriately represented in order to aid decision making.	As we state in our qualifying statement for the recommendation on p81 (line 2-4), there was no strong evidence of comparative clinical effectiveness for any of the bisphosphonates. In addition there was conflicting health economic evidence over which bisphosphonate was the most cost-effective, although as a class of drugs they do seem to be cost-effective. The GDG therefore felt that it was not possible to recommend a specific bisphosphonate. Rosen et al. 2004 is retrospective sub-group analysis of data from Rosen et al. 2001. Rosen et al. 2001 was an equivalence study of 1500 patients. It only recruited 1100 patients so was underpowered and was only designed to show equivalence of the interventions. Therefore the GDG do not feel that this trial can be used as the basis for changing the recommendation as you suggest.
SH	Novartis Pharmaceuticals UK Ltd	161.3	Full version	81	2-7	The Guidelines state "The choice of which bisphosphonate to use for patients with bone metastases should be a local decision, taking in to account patient preference and limited to preparations licensed for this indication." We fully support the importance of patient preference and its acknowledgement within the guideline. However, in order to support informed decision making both for the patient and clinician it is important that the guideline comprehensively and	The guideline is not intended to be a textbook of medicine. This level of detail about the pros and cons of each bisphosphonate can be found in the BNF.

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						accurately reflects the relevant evidence with regard to the pros and cons of each bisphosphonate.	
SH	Novartis Pharmaceuticals UK Ltd	161.4	Full version	81	31-32	The draft guideline states that no bisphosphonate is better than the others in any respect. From the evidence detailed above in this document, this is clearly not the case. As described previously, there is a wealth of independent high quality publications to show that nitrogen-containing bisphosphonates ibandronate, pamidronate and zoledronate are superior to previous generations of bisphosphonates and this is supported by clinical Guidelines including Aapro et al 2007, ASCO 2003 Guidelines in the role of bisphosphonates and bone health issues in women with breast carcinoma. As such there is a clear difference within the group. It is also true that the Aapro et al Guideline on solid tumours (in the section on breast cancer) refer to the superiority of zoledronate over pamidronate, based on the data from the Rosen 2003 paper. The Aapro et al Guideline 2007 also highlights the key table from the Cochrane Review meta-analysis which shows that when compared against placebo zoledronic acid has the greatest overall reduction in the risk of SREs. In addition in the results section of the same Cochrane Review it states that zoledronic acid and pamidronate are supported by the most convincing evidence of benefit. It is important that this guideline acknowledges these findings. The ASCO 2003 Guidelines also only make reference to zoledronate and pamidronate as treatment options. Interestingly neither clodronate or ibandronate have regulatory approval for this indication in the USA.	As we state in our qualifying statement for the recommendation on p81 (line 2-4), there was no strong evidence of comparative clinical effectiveness for any of the bisphosphonates. In addition there was conflicting health economic evidence over which bisphosphonate was the most cost-effective, although as a class of drugs they do seem to be cost-effective. The GDG therefore felt that it was not possible to recommend a specific bisphosphonate. Rosen et al. 2004 is retrospective sub-group analysis of data from Rosen et al. 2001. Rosen et al. 2001 was an equivalence study of 1500 patients. It only recruited 1100 patients so was underpowered and was only designed to show equivalence of the interventions. Therefore the GDG do not feel that this trial can be used as the basis for changing the recommendation as you suggest. It is not standard NICE methodology to use other guidelines as the evidence base for recommendations in NICE guidelines. If there is a high-quality meta-analysis within a guideline we may appraise it and. include this in the evidence that the GDG will consider when agreeing recommendations.
SH	Novartis Pharmaceuticals UK Ltd	161.5	Full version	82	42-46	There has been an update of cost effectiveness by Mark Botteman in 2006. Results from this analysis	The Botteman paper (2006) was included in the review of the economic evidence for this topic.

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						using a UK perspective demonstrate that zoledronate is the most cost-effective bisphosphonate. This is an important consideration when deciding which bisphosphonate to recommend. The analysis demonstrated that zoledronic acid was more effective and less expensive than all other compounds (oral and IV ibandronate, clodronate, IV pamidronate).	However it consists of a series of pairwise comparisons, comparing each bisphosphonate therapy against no therapy; and therefore the analysis shown is not a true incremental approach (since each intervention is not compared to the next best). The guideline development group were therefore advised that the evidence as to which bisphosphonate is most cost-effective is not clear on the basis of the current evidence base.
SH	Novartis Pharmaceuticals UK Ltd	161.6	Full version	81	7	In direct contradiction of the point on line 7 p.81 that states there is no evidence for comparative clinical efficacy. The Rosen et al 2003 paper, the Cochrane Review 2005, the ASCO 2003 Guidelines and the Aapro Clinical Guideline 2007, all suggest that at the licensed doses, zoledronate and pamidronate confer statistically significant benefits across multiple end points. These data indicate that zoledronate and pamidronate are the most appropriate bisphosphonates for treating breast cancer patients. In addition the Rosen et al 2003 data suggests that zoledronate may confer advantages over pamidronate. In addition, the health economic analysis by Botteman et al 2008 demonstrates that zoledronic acid is more cost-effective than pamidronate (or any other bisphosphonate), and this is likely to be because of the shorter infusion time, again supported by the work of Chern et al 2004.	As we state in our qualifying statement for the recommendation on p81 (line 2-4), there was no strong evidence of comparative clinical effectiveness for any of the bisphosphonates. In addition there was conflicting health economic evidence over which bisphosphonate was the most cost-effective, although as a class of drugs they do seem to be cost-effective. The GDG therefore felt that it was not possible to recommend a specific bisphosphonate. Rosen et al. 2004 is retrospective sub-group analysis of data from Rosen et al. 2001. Rosen et al. 2001 was an equivalence study of 1500 patients. It only recruited 1100 patients so was underpowered and was only designed to show equivalence of the interventions. Therefore the GDG do not feel that this trial can be used as the basis for changing the recommendation as you suggest. We were unable to identify the paper Botteman et al 2008 and assume that you are referring to Botteman et al 2006. The Botteman (2006) paper was included in the review of the economic evidence for this topic. However it consists of a series of pairwise comparisons, comparing each bisphosphonate therapy against no therapy; and therefore the analysis shown is not a true incremental approach (since each intervention is

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							not compared to the next best). The guideline development group were therefore advised that the evidence as to which bisphosphonate is most cost-effective is not clear on the basis of the current evidence base.
SH	Novartis Pharmaceuticals UK Ltd	161.7	Full version references			REFERENCES 1] Hillner et al. (2001) American Society of Clinical Oncology 2003 Update on the Role of Bisphosphonates and Bone Health Issues in Women With Breast Cancer. *Journal of Clinical Oncology*, Vol 21, Issue 21: 4042-4057 2] Hortobadgyi et al. (1998) Long-term-preventions of skeletal complications of mtastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. J Clin Oncology; 16: 2038-2044. 3] Hei Y, Saad F, Coleman RE et al. (2005) Fractures negatively affect survival in patients with bone metastases from breast cancer. Breast Cancer Res Treat;94(suppl 1):S260 4] Emkey R.D. et al. (2006) Improving compliance and persistence with bisphosphonate therapy for osteoporosis. American Journal of Medicine. Vol 119; 185-245. 5] Paterson A.H.G. et al. (1993) Double-blind controlled trials of oral clodronate in patients with bone metastases from breast cancer. Journal of Clinical Oncology. Vol. 11; 59-65. 6] AG Robertson et al. (1995) Effect of oral clodronate on metastatic bone pain: a double-blind, placebo-controlled study. Journal of Clinical Oncology, Vol 13, 2427-2430. 7] R. E. Coleman. (1999) Double-blind, randomised,	Studies 1, 2, 5, 6, 8, 15 and 17 were included in the guideline (Warr *et al.* 2002). Studies 3, 10, 13 and the product summaries do not appear to be peer reviewed journal articles. Study 11 is a non-systematic review with consensus statement. Study 12 is a pre-clinical paper. Studies 4 and 9 relate to women with osteoporosis (not breast cancer). This population is not relevant to the PICO question. Studies 7, 14 and 16 have outcomes which are not relevant to the PICO question. Study 18 was included in the health economics evidence.

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						placebo-controlled, dose-finding study of oral ibandronate in patients with metastatic bone disease. *Annals of Oncology* 10:311-316. 8] Body J.J. et al. (2004) oral ibandronate reduces the risk of skeletal complications in breast cancer patients with metastatic bone disease: results from two randomised, placebo-controlled phase III studies. British Journal of Cancer. Vol. 90; 1133-1137. 9] L. B. Tanko et al. (2003) The efficacy of 48-week oral ibandronate treatment in postmenopausal osteoporosis when taken 30 versus 60 minutes before breakfast. Bone; Vol. 32; 421-426. 10] Heatley et al (2006) Gastrointestinal side effects can reduce compliance with oral bisphosphonate therapy in cancer patients. Poster presented at EONS; Poster 16. 11] Aapro et al (2007) Guidance on the use of bisphosphonates in solid tumours; recommendations of an international expert panel. Annals of Oncology. Vol 19; 420-432. 12] Green et al (1994) preclinical pharmacology of CGP 42'446, a new, potent, heterocyclic bisphosphonate compound. Journal of Bone and Mineral Research. Vol. 9; 745-751. 13] Joshua D.E. et al (2002) Resource used by zoledronic acid or pamidronate infusions in multiple myeloma and cancer. 100; 496B: Abstract 5571. 14] Chern B. et al (2004) Bisphosphonate infusions: patient preference, safety and clinical use. Support Cancer Care. Vol. 12. 463-466. 15] Rosen et al (2003). Long term efficacy and safety	

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						of zoledronic acid compared with pamidronate disodium in the treatment of skeletal complications in patients with advanced multiple myeloma or breast carcinoma. Cancer. Vol. 98: 1735-1744. 16] R. J. Cook, P. Major. (2001) Methodology for Treatment Evaluation in Patients With Cancer Metastatic to Bone. JNCI Journal of the National Cancer Institute. 93(7):534-538. 17] Pavlakis et al (2005) Bisphosphonates for breast cancer (review)The Cochrane Collaboration. 18] Botteman et al (2006) Cost effectiveness of bisphosphonates in the management of breast cancer patients with bone metastases. Annal of Oncology. 17 (7): 1072-1082. Summary of products characteristics for Bondronat film coated tablets. Printed October 2008. Summary of products characteristics for Bondronat concentrate for solution for infusion. PrintedOctober 2008. Summary of products characteristics for Bonefos capsules. Printed October 2008. Summary of products characteristics for Bonefos Concentrate. Printed October 2008. Summary of products characteristics for Aredia 90mg. Printed October 2008. Summary of products characteristics for Zometa 4mg/5ml concentrate. Updated 25.01.2008.	
SH	Nucletron B.V.	162				This organisation was approached but did not respond.	
SH	Nutrition Society	163				This organisation was approached but did not respond.	
SH	Organon Laboratories Limited	164				This organisation was approached but did not respond.	
SH	Ortho Biotech	165				This organisation was approached but did not	

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						respond.	
SH	Ovarian Cancer Action	166				This organisation was approached but did not respond.	
SH	Oxford Nutrition Ltd	167				This organisation was approached but did not respond.	
SH	Peninsula Clinical Genetics Service	168				This organisation was approached but did not respond.	
SH	PERIGON Healthcare Ltd	169				This organisation was approached but did not respond.	
SH	Pfizer Limited	170.0	General			More data has been published on Exemestane in the advanced breast cancer. *Reference:* Paridaens RJ et al. Phase III study comparing Exemestane with Tamoxifen as first line hormonal treatment of metastatic breast cancer in postmenopausal women: The European Organisation for Research and Treatment of Cancer (EORTC). *Journal of Clinical Oncology.* Published Ahead of Print on September 15, 2008 as 10.1200/JCO.2007.14.4659	In accordance with NICE methodology, each guideline has a cut-off-date for reviewing evidence. The evidence you cite here was published after our cut off date and therefore is not able to be included in the evidence review for the guideline.
SH	Pfizer Limited	170.1	Full version	47	6-8	To our knowledge, there are currently no systems/guidelines in place to monitor peri-menopausal women, so that they are put on appropriate treatment once they become (post) menopausal. We believe that updating this guideline gives an opportunity to make a recommendation in this area.	We have offered what we hope will be a useful working definition of postmenopausal patients in the context of these therapies.
SH	Pierre Fabre Limited	171.0	Full version	61	10-12	The option to change the chemotherapy in patients that progress with trastuzumab + docetaxel should also be considered in the research programme. Alternative chemotherapy may control tumour progression after docetaxel failure while patients still benefit from trastuzumab. There is evidence of synergy and high activity of vinorelbine plus trastuzumab. This would also be consistent with the management of advanced disease for Her2 –ve patients (page 22 line 2) and research	We have not specified chemotherapy/biological therapy combinations in the research recommendation because there are many possible combinations and we did not think it appropriate to be prescriptive over which combinations were investigated.

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						recommendations (page 61 line 10)	
SH	Pierre Fabre Limited	171.1	Full	22	2	Docetaxel is increasingly used in the adjuvant setting and patients that present with advanced disease have often been exposed to anthracycline and taxane. The use of an alternative taxane or earlier use of subsequent agents (vinorelbine or capecitabine) should be clarified. There is some evidence and clinical experience indicating useful activity with vinorelbine plus capecitabine. This will offer an alternative combination to docetaxel combinations if appropriate for particular patients with very aggressive disease. The combination of vinorelbine + capecitabine is included in the ESMO recommendations (Esmo Guidelines Working Group, Ann Oncol 2008).	Published evidence about the activity of vinorelbine plus capecitabine was included in the evidence appraisal considered by the GDG. The GDG was not persuaded that the evidence for this combination was sufficiently strong to include it in the recommendations.
SH	Pierre Fabre Limited	171.2	Full	22	2	Patients who are Her2 +ve may have tumour cell lines that are resistant to docetaxel but could continue to benefit from trastuzumab if the cytotoxic chemotherapy were changed. The option to continue trastuzumab and change the chemotherapy is considered as a research recommendation (page 61 line10). There is evidence from the literature review of synergy between vinorelbine and trastuzumab (p 54, line 16) making vinorelbine a good candidate for this research.	We have not specified chemotherapy/biological therapy combinations in the research recommendation because there are many possible combinations and we did not think it appropriate to be prescriptive over which combinations were investigated.
SH	Pierre Fabre Limited	171.3	Full	44	11	The availability of an oral equivalent to intravenous treatment has major implication for the time the patient has to spent in hospital to receive their treatment and is also a factor for patients to consider.	It is unfortunate that there is a lack of proper randomised comparisons of these agents with intravenous preparations. We do not feel that a change to the text would be helpful at this point.
SH	Pierre Fabre Limited	171.4	Full	54	1	The dose limiting toxicity for vinorelbine is neutropenia. This is of short duration (5-7 days), rapidly reversible and non-cumulative. The time the patient is at risk of infection is therefore relatively short. This explains why the incidence of grade 3/4 neutropenia (43% SmPC) is associated with a lower neutropenic infection rate (3% SmPC). The relative incidence of neutropenia should be kept in perspective with other treatments for breast cancer (e.g. docetaxel 76.4% G4 SmPC). For many patients,	Thank you for your comments. This text is a summary of the evidence that was appraised, which cited that neutropenia was a common adverse event in these patients. Isolated neutropenia is rarely in itself of clinical significance for patients, whereas febrile neutropenia is a much more serious treatment complication.

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				71	16-47	neutropenia can be event-free but for some, prompt intervention is essential. Cancer Centres have specialist doctors, nurses and pharmacists that are trained to recognise signs and symptoms of toxicity or infection and react appropriately and promptly. This institutional competence is essential for a safe and effective cancer service. Strategies that move treatment closer to the patient or allow treatment at home should retain and extend this institutional competence.	These factors will clearly need to be considered when the recommended research is performed
SH	Pierre Fabre Limited	171.5	Full	71	16 - 42	The treatment of patients closer or in their own home is a key feature of the Cancer Reform Strategy. The delivery of cancer treatment is a specialised nursing procedure and requires access to specialised hospital support. Cancer is a relatively small proportion of the primary care workload making the cost and sustainability of training, retention, workload management, consistency and accountability of a community-based service provision very ambitious. An alternative strategy to move treatment closer to the patients home is through nurse led outreach services from the cancer centre using oral cytotoxic treatments. Responsibility for Oncology nurse expertise and training remains integrated and managed by the cancer centre or unit. The out-of-hours infrastructure for the management of toxicity is integrated with the diagnostic and medical expertise of the cancer specialists. Both vinorelbine and capecitabine are oral cytotoxic treatments that can be administered outside the hospital in outreach clinics or in the patients' own home (with direct telephone communication from the specialist nurse). The goal of treatment closer or in the patients' home can be more easily achieved with oral chemotherapy and the security and accountability of a specialist service is retained. The health economics for oral vinorelbine in short outpatient clinics (30 minutes), outreach and	Thank you for your comments. As you will notice from the guideline, there is not enough evidence available on this topic to enable the GDG to make a recommendation. We have therefore made a research recommendation instead.

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						domiciliary use are positive (v intravenous vinorelbine). Examples of the logistical issues mentioned in section 5 have already been addressed and documented by NHS cancer centres. The use of oral chemotherapy removes many practical constraints associated with iv treatments. NHS or private providers can be commissioned for these outreach services.	
SH	Pierre Fabre Limited	171.6	Full	72	31	Both vinorelbine and capecitabine are oral chemotherapy agents. Oral chemotherapy does not require the hospital infrastructure (pharmacy reconstitution and chemotherapy chairs) that is required for intravenous treatment. Modernising the treatment pathway to deliver care closer to the patient (outreach or at home) requires clear management to align medical, pharmacy and nursing working arrangements but are less costly, more efficient and preferred by most patients. Capacity increases of 38% have been reported.	Use of both oral chemotherapies requires haematologic and biochemical monitoring, and therefore still requires some access to the hospital infrastructure. We have amended the research recommendation to include oral chemotherapies.
SH	Pierre Fabre Limited	171.7	Full	72	33	This research question should consider patient preference for oral vs intravenous treatment.	We do not think this change is necessary.
SH	Pierre Fabre Limited	171.8	Full	96	7	The health economics for a modified service using oral vinorelbine is very favourable and should also be considered.	Yes, oral vinorelbine might be a suitable comparator. Unfortunately we did not find any clinical evidence of its effectiveness. As such it was not included in the economic model.
SH	Pierre Fabre Limited	171.9	Full	108	1-18	Oral vinorelbine is also available and associated with lower cost for administration and alternative models of service delivery (outreach, home use with direct telephone contact with the specialist nurse). Oral vinorelbine was assessed as less costly than an intravenous vinorelbine service despite higher drug acquisition cost.	Again, since we did not find any clinical evidence on the effectiveness of oral vinorelbine it was not included as a comparator in the model.
SH	Primary Care Pharmacists' Association	172				This organisation was approached but did not respond.	
SH	Princess Alexandra Hospital NHS Trust	173				This organisation was approached but did not respond.	

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SH	Queen Elizabeth Hospital NHS Trust (Woolwich)	174				This organisation was approached but did not respond.	
SH	Queen Victoria Hospital NHS Trust	175				This organisation was approached but did not respond.	
SH	Roche Diagnostics	176				This organisation was approached but did not respond.	
SH	Roche Products Limited	177.0	Full	General		We suggest that descriptors of HER2 testing methodology and scoring should be addressed throughout the document. Only IHC (immunohistochemistry) techniques are scored as 0 – 3+. This should be specified in order to prevent confusion. IHC scores of 0 and 1+ are classed as HER2 normal (or negative). A score of 3+ is classified as HER2 positive. Scores of 2+ are classed as equivocal and require further testing by in-situ hybridisation techniques such as FISH, CISH or SISH. (Fluorescence /Chromogenic/ Silver-enhanced in situ hybridisation). Approximately 25% of IHC2+ tumours will be ISH+. There is no mention of ISH techniques within the document. The recent guideline publication in the Journal of Clinical Pathology gives a very comprehensive overview of current recommendations for HER2 testing in the UK. Reference: • Walker RA et al. HER2 testing in the UK: further update to recommendations. J Clin Pathol 2008; 61: 818–824	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines. TA34 was published in 2002, and we acknowledge that the guidelines for HER2 testing have changed since that time. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	Roche Products Limited	177.09	Full	27	29	Typographical error: Trastuzumab spelt incorrectly	Thank you. This has been corrected.

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SH	Roche Products Limited	177.1	Full	44	36-38	*'Endocrine therapy should be offered to patients with ER+ tumours as 1st line therapy.'* This does not take into account the value of adding trastuzumab to an aromatase inhibitor in ER+/HER2+ (co-positive) tumours. Approximately, 50% of HER2+ breast cancers are also ER+. Evidence suggests HER2 overexpression is associated with resistance to hormone therapy (ref Jones 2003, Johnston 2007, Orman 2007) due to crosstalk between HER2 and ER signalling pathways (Osborne CK Clin Cancer Res 2001; 7 (Suppl);4338s-4342s; Dowsett Endocrin Relat Cancer 2001; 8:191-195). The Tandem study (Tandem, Kaufman B, et al ESMO 2006 Abstract LBA2; Mackey et al SABCS 2006, Abs 3) randomised postmenopausal women with HER2+ and ER+ breast cancer to receive either anastrozole alone or anastrozole in combination with Trastuzumab as first-line treatment for MBC. The primary endpoint was progression-free survival (PFS). The addition of Trastuzumab to anastrozole significantly improved PFS from 2.4 to 4.8 months (HR 0.63; p=0.0016) for women with HER2 and HR co-positive MBC. Furthermore, overall response rate tripled (from 6.8% to 20.3%; p=0.018) and clinical benefit rate increased by 53% (27.9% to 42.7%; p=0.026) with addition of Trastuzumab to anastrozole compared with anastrozole alone. Despite 70% of patients who progressed on anastrozole alone receiving Trastuzumab after progression, there was a 4.6 month improvement in overall survival (23.9 to 28.5; p 0.325). In addition, a post hoc analysis indicated a median OS benefit of	The Tandem trial has not been published in a peer reviewed publication. Trastuzumab in combination with AIs is on the list of topics being considered by the NICE Topic Selection Panel for Cancer as a future STA. We have therefore not investigated this combination within the guideline.

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						11.3 months for patients who received anastrozole plus Trastuzumab (n=103) vs anastrozole alone and did not cross over to receive Trastuzumab at disease progression (n=31) (28.5 vs 17.2 months, p=0.0479). There were no new or unexpected AEs associated with the addition of Trastuzumab to anastrozole. The results of the Tandem trial demonstrate that the combination of Trastuzumab plus anastrozole significantly improves PFS, ORR, CBR, and may prolong OS compared with anastrozole alone in women with HER2 and HR co-positive MBC. This suggests that simultaneous targeting of both pathways improves outcomes over hormone therapy alone in co-positive MBC.	
SH	Roche Products Limited	177.10	Full	32	43	Additional point recommended: Add 'long disease free interval' to bullet points No mention of core vs excision biopsies	We disagree. The bullet points are examples only, they are not meant as an exhaustive list. Also in many clinical situations where multiple metastases are present, a long disease free interval would not be considered an indication for re-biopsy. The mode of biopsy, if necessary, will be determined by clinical circumstance and can't be determined by this guideline
SH	Roche Products Limited	177.11	Full	42	22	Adjuvant on line Adjuvant on line is not relevant in the treatment of metastatic breast cancer. Additionally, it does not currently include HER2 status – the poor prognosis of these patients and the benefit of trastuzumab is not represented. Care needs to be taken that a patient is not misled by this tool – potentially a more optimistic outcome could be anticipated than is actually the case.	We agree that Adjuvant Online is not a specific decision making tool for use in metastatic breast cancer. This text relates to the evidence review and is not a recommendation.
SH	Roche Products Limited	177.12	Full	44	16	*biological response modifiers* The term 'biological response modifiers' implies that these treatments modify the response to another	We will change the text to refer to "biological therapy"

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						agent. We would prefer 'biological therapy'	
SH	Roche Products Limited	177.13	Full	44	42	*Co-Positive (ER+/HER2+) Tumours* The recommendations for the 1st line treatment of ER+ mBC should include the use of trastuzumab for HER2+ patients, based upon the data detailed below: HER2+ patients with advanced breast cancer should receive trastuzumab in combination with a taxane first-line; irrespective of ER status. References: • Slamon DJ et al 2001 NEJM; 344; 783-792 • Marty M et al JCO 2005: 23; 4265-4274 • Marty M et al SABCS 2006 • Wardley A et al SABCS 2007 • Robert N et al 2006 JCO; 24: 2786-2792 • Bullock Oncologist 2008 • Pegram M et al ASCO 2007 or as monotherapy if not suitable for chemotherapy. • Vogel C, et al. JCO 2002;20:719–26 Trastuzumab plus docetaxel should be used first line in HER2+ mBC as per license (Trastuzumab SmPC); other combinations have been shown to be effective, though are off-label. RCT data from the TanDem study indicate improved response rates and duration of response in HER2 positive tumours if trastuzumab is added in to endocrine therapy. The endocrine treatment recommendation algorithm already includes the option to add in chemotherapy if a rapid response is required. It should also include the option to add in trastuzumab for the inevitably	We are uncertain whether you are recommending that all patients with ER-positive disease should receive first-line treatment with trastuzumab in combination with a taxane or that they should receive treatment with trastuzumab plus an aromatase inhibitor if they are postmenopausal. Trastuzumab in combination with AIs is on the list of topics being considered by the NICE Topic Selection Panel for Cancer as a future STA. We have therefore not investigated this combination within the guideline.

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						higher-risk HER2 positive tumours. The best responses to trastuzumab are seen in the first line setting irrespective of HR status. Approximately, 50% of HER2+ breast cancers are also ER+. Evidence suggests HER2 overexpression is associated with resistance to hormone therapy (ref Jones 2003, Johnston 2007, Orman 2007) due to crosstalk between HER2 and ER signalling pathways (Osborne CK Clin Cancer Res 2001; 7 (Suppl);4338s-4342s; Dowsett Endocrin Relat Cancer 2001; 8:191-195) The Tandem study (Tandem, Kaufman B, et al ESMO 2006 Abstract LBA2; Mackey et al SABCS 2006, Abs 3) randomised postmenopausal women with HER2+ and ER+ breast cancer to receive either anastrozole alone or anastrozole in combination with Trastuzumab as first-line treatment for MBC. The primary endpoint was progression-free survival (PFS). The addition of Trastuzumab to anastrozole significantly improved PFS from 2.4 to 4.8 months (HR 0.63; p=0.0016) for women with HER2 and HR co-positive MBC. Furthermore, overall response rate tripled (from 6.8% to 20.3%; p=0.018) and clinical benefit rate increased by 53% (27.9% to 42.7%; p=0.026) with addition of Trastuzumab to anastrozole compared with anastrozole alone. Despite 70% of patients who progressed on anastrozole alone receiving Trastuzumab after progression, there was a 4.6 month improvement in overall survival (23.9 to 28.5; p 0.325). In addition, a post hoc analysis indicated a median OS benefit of 11.3 months for patients who received anastrozole plus Trastuzumab (n=103) vs anastrozole alone and did not cross over to receive Trastuzumab at disease	

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						progression (n=31) (28.5 vs 17.2 months, p=0.0479) There were no new or unexpected AEs associated with the addition of Trastuzumab to anastrozole. The results of the Tandem trial demonstrate that the combination of Trastuzumab plus anastrozole significantly improves PFS, ORR, CBR, and may prolong OS compared with anastrozole alone in women with HER2 and HR co-positive MBC. This suggests that simultaneous targeting of both pathways improves outcomes over hormone therapy alone in co-positive MBC.	
SH	Roche Products Limited	177.14	Full	50	45	*Capecitabine/docetaxel (XT) combination* For patients with LABC/MBC whose disease needs to be quickly controlled, the combination of XT should be considered an option first-line in patients who have received an anthracycline/unsuitable, e.g. fit patients who have high disease burden and/or rapidly progressing disease. The qualifying statement does not appreciate the statistical significance and clinical relevance of the O'Shaughnessy XT data. Although there was a higher number of grade 3 and 4 toxicities for those patients receiving XT, overall QoL scores were better – showing the advantage of effective chemotherapy in reducing the impact of tumour burden on QoL. Reference: • O'Shaughnessy J et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda®) vs. a reference arm of intravenous CMF (cyclophosphamide, methotrexate and 5-fluorouraeil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001;12:1247–54.	The reference you have cited does not look at the combination of capecitabine/docetaxel. The GDG were aware of the O'Shaughnessy XT data when these recommendations were made. We therefore do not feel that a change to the recommendation is needed.

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SH	Roche Products Limited	177.15	Full	51	47-48	lack of significant risk reduction with taxanes The exception to this statement being docetaxel combined with capecitabine combined therapy. A phase III registration trial by O'Shaughnessy 2002 showed a 3 month significant survival advantage with this combination compared with single-agent docetaxel.	The O'Shaughnessy et al., 2002 trial was the pivotal trial in TA62. The advanced breast cancer guideline was tasked with updating TA62 and therefore only considered evidence published post 2002, hence the O'Shaughnessy 2002 trial is not included in the evidence base for this guideline. This statement derives from Carrick et al. (2005) a high quality systematic review. There is reference (p 52 lines 8-12) to the studies by Leonard et al., 2006 and Miles et al., 2004 outlining the advantages of combining docetaxel with capecitabine.
SH	Roche Products Limited	177.16	Full	52	23-24	*ordering of chemotherapy* There is evidence to suggest capecitabine improves overall survival compared with vinorelbine and may also be cost-effective versus vinorelbine. Therefore capecitabine should be placed above vinorelbine in the treatment pathway. References: • Verma S et al. Palliative chemotherapy with vinorelbine or capecitabine in women anthracycline- and taxane- refractory metastatic breast cancer. Curr Oncol 2004; 11 (2): 63-67. • Miles D et al. Survival benefit with capecitabine/docetaxel versus docetaxel alone: Analysis of therapy in a randomized phase III trial. Clin Breast Cancer 2004; 5 (4): 273-278. • Jones, L et al. Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer. Health Technology Assessment 2004; 8(5).	The evidence cited was all considered in the formulation of the health economic model. The results of the model show that strategies with vinorelbine as second line therapy, followed by capecitabine as third line were more cost-effective (than when used the other way around) in the base case analysis. However the uncertainty around this result was such that the guideline development group felt they could not prescribe the order of delivery of these agents after first-line chemotherapy.

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SH	Roche Products Limited	177.17	Full	52	18	*1st line use of capecitabine/XT* In the recommendations for lines of chemotherapy treatment, no reference is made to the first line use of capecitabine in those patients who have received an anthracycline and taxane in the adjuvant setting. The use of adjuvant docetaxel in higher risk patients is growing rapidly, (as per NICE guideline September 2006) so this situation will arise more often in the future. There is no mention of use of docetaxel/capecitabine combination in 1st line treatment, (as per NICE guidance May 2003) for those patients with a good performance status.	We have not looked at the evidence for the use of docetaxel or capecitabine in patients who have received adjuvant docetaxel, but we are not aware of any randomised phase III trial data in this area. Therefore we are not able to make recommendations on this and it will need to be a matter for clinical judgement. This guideline was tasked with updating technology appraisal 62. As such the recommendations from TA 62 have been replaced by the recommendations in this guideline.
SH	Roche Products Limited	177.18	Full	52	23-25	*Ordering of 2nd line and 3rd line options* The ordering of vinorelbine and capecitabine implies 2nd line vinorelbine and 3rd line capecitabine. Current clinical practice, cost-effectiveness evidence, and data would favour the opposite order. Suggest alphabetical ordering in line with usual NICE practice.	NICE editors have not commented on this style issue so we will leave the text as is.
SH	Roche Products Limited	177.19	Full	54	5	Error: The Chan 2005 study compared gemcitabine/docetaxel with capecitabine/docetaxel not capecitabine/docetaxel with gemcitabine.	This typographical error has been corrected.
SH	Roche Products Limited	177.2	Full	52	18-25	*Sequence of chemotherapies for MBC patients* To help provide greater clarity regarding treatment strategies Roche suggests that this section should be divided into HER2+ and HER2- patients as treatment strategies will undoubtedly vary according to HER2 status: For HER2+ patients options should include retreatment with trastuzumab for reasons outlined further below. HER2- patients need to be stratified by previous treatment (anthracycline; anthracycline and taxanes;	Patients have been stratified according to HER2 status in the algorithm on p 22 of the full version. We do not feel that further recommendations are needed on this. Trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data. We encourage Roche to provide this data for review.

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						taxanes; neither). Ordering of capecitabine and vinorelbine in the document implies that vinorelbine should be used 2nd line and capecitabine 3rd line. However, evidence listedbelow suggests capecitabine improves survival over vinorelbine post-taxane and may also be cost-effective versus vinorelbine (Jones L et al, 2004). Therefore capecitabine should be placed above vinorelbine in the treatment pathway. References: • Miles D et al. Survival benefit with capecitabine/docetaxel versus docetaxel alone: analysis of therapy in a randomized phase I11 Trial. Clinical Breast Cancer 2004; 5 (4): 273-278. • Verma S et al. Palliative chemotherapy with vinorelbine or capecitabine in women with anthracycline- and taxane- refractory metastatic breast cancer. Current Oncology 2004; 11 (2P): 63-67. • Mavroudis D et al. A multicenter randomized study comparing vinorelbine plus gemcitabine versus capecitabine monotherapy as salvage treatment in patients with advanced breast cancer pretreated with taxane and anthracycline chemotherapy: a preliminary report. J Clin Oncol 2006; 24 (18S): Abstract 658).	The recommendation does not imply that one agent should be used before the other. It states that either vinorelbine or capecitabine should be used 2nd line and then either capecitabine or vinorelbine should be used 3rd line (depending on which agent was used 2nd line). The evidence cited was all considered in the formulation of the health economic analysis. The results of this analysis have guided the recommendations.

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						• Jones, L et al. Systematic review of the clinical effectiveness and cost-effectiveness of capecitabine (Xeloda®) for locally advanced and/or metastatic breast cancer. Health Technology Assessment 2004; 8(5). If patients have been treated with an adjuvant taxane (node positive) or are taxane unsuitable, then capecitabine may be used first-line in MBC, as supported by the following evidence base References: • Talbot et al. Br J Cancer 2002;86:1367-72. • O'Shaughnessy, et al. Ann Oncol 2001;12:1247-54 • Stockler ASCO 2007 Abs 1031 • Bajetta et al. JCO 2005;23:2155–61	
SH	Roche Products Limited	177.20	Full	54	33-37	capecitabine monotherapy data The four capecitabine pivotal monotherapy trials demonstrate consistent outcomes in 498 patients. Based on these data the EMEA granted a licence for capecitabine monotherapy in metastatic breast cancer, and NICE subsequently granted positive guidance. We dispute the comment that these studies are 'poor' and 'should be interpreted with caution'. • Blum JL et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 1999; 17: 485-493. • Blum JL et al. Multicenter, phase II study of capecitabine in taxane-pre-treated metastatic breast carcinoma patients. Cancer 2001; 92: 1759-1768. • Reichardt P et al. Multicenter phase II study of oral capecitabine (Xeloda) in patients with metastatic breast cancer relapsing after	The two papers by Blum *et al.* were included in the original TA62. The advanced breast cancer guideline was tasked with updating TA62 and therefore only considered evidence published post 2002, hence these trials are not included in the evidence base for this guideline. Fumoleau *et al.* (2004) and Reichardt *et al.* (2003) were both well conducted and well reported phase II studies. The evidence base as a whole was 'poor' because there were no systematic reviews, meta-analyses, RCTs or other comparative studies to inform those persons making recommendations for the guideline. The evidence statement has been amended for clarification.

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						treatment with a taxane-containing therapy. Ann Oncol 2003; 14: 1227-1233. • Fumoleau P et al. Multicentre, phase II study evaluating capecitabine monotherapy in patients with anthracycline- and taxane-pretreated metastatic breast cancer. Eur J Cancer 2004; 40: 536-542.	
SH	Roche Products Limited	177.21	Full	54	40-43	Missing data This section on capecitabine monotherapy does not include a number of key papers. • Blum JL et al. Multicenter phase II study of capecitabine in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 1999; 17: 485-493. • Blum JL et al. Multicenter, phase II study of capecitabine in taxane-pre-treated metastatic breast carcinoma patients. Cancer 2001; 92: 1759-1768. • Largillier R et al. Long median survival with capecitabine (X) single-agent therapy for patients (pts) with anthracycline- and taxane-pretreated metastatic breast cancer (MBC). Am Soc Clin Oncol 2006; Abstract 10710. • Seidman AD et al. Single-agent capecitabine: A reference treatment for taxane-pretreated metastatic breast cancer? The Oncologist 2002; 7 (6): 20-28. • Lomas M et al. Safety of long-term administration of capecitabine in metastatic breast cancer patients. Am Soc Clin Oncol 2006; Abstract 10755.	The two papers by Blum *et al.* were included in the original TA62. The advanced breast cancer guideline was tasked with updating TA62 and therefore only considered evidence published post 2002, hence these trials are not included in the evidence base for this guideline. Seidman *et al.* (2002) is a non-systematic review and was not selected for appraisal. Largillier *et al.* (2006) and Lomas *et al.* (2006) are meeting abstracts and as such were not selected for appraisal.
SH	Roche Products Limited	177.22	Full	55	8-11	study selection The O'Shaughnessy 2002 study should be included her rather than the Chan 2005 study. The Chan 2005 study did not reach its primary endpoint of	The O'Shaughnessy et al., 2002 trial was the pivotal trial in TA62. The advanced breast cancer guideline was tasked with updating TA62 and therefore only considered evidence published post 2002, hence the O'Shaughnessy 2002 trial is not

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						progression-free survival and thus was a negative study.	included in the evidence base for this guideline.
SH	Roche Products Limited	177.23	Full	58	30	*terminology* As per previous comment (#13 above) - the term 'biological response modifiers' implies that these treatments modify the response to another agent. We would prefer 'biological therapy'.	We have made this change
SH	Roche Products Limited	177.24	Full	59	11	*Trastuzumab mode of action* Trastuzumab's mode of action is more complex than simply blocking the receptor. In addition to this action it also has anti-angiogenic properties, prevents cleavage of the HER2 receptor and hence the constant growth signal transmission, as well as recruiting the patient's own immune system to attack the tumour cells via ADCC (antibody dependant cellular cytotoxicity). Reference: • Nahta R, Esteva FJ. Trastuzumab: mechanisms of action and resistance. Cancer Letters 2006; 232: 123-138	The GDG appreciate this but felt that this level of detail was not appropriate for the background information.
SH	Roche Products Limited	177.25	Full	59	16	*Blood Brain Barrier* Contrary to the statement in the guideline, emerging data (Bartsch 2007) show that the administration of radiotherapy to the brain disrupts the blood brain barrier enough to allow the passage of large molecules such as trastuzumab.	This text is background information covering the generality of treatment with biological therapies. It does not specifically consider individuals who have been treated with radiotherapy to the brain. We are aware this is a topic of current NCRN supported research in the UK.
SH	Roche Products Limited	177.26	Full	59	21	*EGFR Receptor* There is no evidence for the activity of EGFR in breast cancer. 'Thus far, pure EGFR expression in breast cancer bears no prognostic value and is not a useful predictive factor for therapy in breast cancer.	This text is in the background information and is only intended to briefly describe the mode of action of lapatinib. It is not a recommendation and does not comment on the prognostic value of EGFR expression as a predictive factor for therapy in breast cancer.

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						Standardized methods for its measurement and interpretation are required for further evaluation and for its inclusion in future clinical trials. ' Reference: • Chan SK, Hill ME, Gullick WJ. The role of the epidermal growth factor receptor in breast cancer. J Mammary Gland Biol Neoplasia 2006; 11: 3–11 • Cameron D, lapatinib oral presentation ASCO 2007	
SH	Roche Products Limited	177.27	Full	59	35-36	*docetaxel/trastuzumab combination* This line implies that the docetaxel trastuzumab combination data was rejected by NICE due to lack of data. The 2004 licence variation for the combination was approved by EMEA on the basis of this study and no new data has been published in this setting subsequently. The recommended new appraisal by NICE would still be on the basis of this one RCT. References: • Marty M et al. Randomised Phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. J Clin Oncol 2005; 23(19): 4265-4274 • Extra JM et al. Favourable effect of continued trastuzumab treatment in metastatic breast cancer patients: results from the French Hermine cohort study. San Antonio Breast Cancer Symposium 2006; Abs 2064. www.sabcs.org	The text has been amended to clarify this. The GDG has not rejected the docetaxel/trastuzumab combination, but was unable to adequately appraise it due to an inability to perform robust health economic modelling (as detailed in the revised text). The GDG have suggested to NICE that the combination of trastuzumab and docetaxel be investigated as an STA.

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SH	Roche Products Limited	177.28	Full	59	36	trastuzumab license It is incorrect to state that trastuzumab is only licensed with paclitaxel. Trastuzumab is licensed in combination with docetaxel (2004) and also with aromatase inhibitors (2007). Only the paclitaxel combination has been appraised by NICE.	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines. TA34 was published in 2002, at which time the statement regarding the licensed combinations for trastuzumab was correct, although we acknowledge that this is no longer the case. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	Roche Products Limited	177.29	Full	59	47	*HER2 Testing – methodology and definitions* Descriptors of HER2 testing methodology and scoring need to be addressed throughout the document. Only IHC (immunohistochemistry) techniques are scored as 0 – 3+. This needs to be specified in order to prevent confusion. IHC scores of 0 and 1+ are classed as HER2 normal (or negative). A score of 3+ is classified as HER2 positive. Scores of 2+ are classed as equivocal and require further testing by in-situ hybridisation technique such as FISH, CISH or SISH. (Fluorescence /Chromogenic/ Silver enhanced in situ hybridisation). Approximately 25% of IHC2+ tumours will be ISH+. There is no mention of ISH techniques within the document. 60% of samples from the pivotal trastuzumab trials were retested using FISH. This allowed a	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines.TA34 was published in 2002, and we acknowledge that the guidelines for HER2 testing have changed since that time. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.

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						retrospective analysis of tumor response based on FISH status. In the pivotal phase II trastuzumab single-agent trial, the response rate was 20% in FISH-positive patients and 0% in FISH-negative patients. All patients in the IHC 2+ and 3+ subgroups who responded tested FISH positive. These results suggest that FISH assessment of HER2 gene amplification may allow the selection of all HER2-positive patients who will benefit from trastuzumab therapy. Reference: • Baselga J. Trastuzumab alone or in combination with chemotherapy in the treatment of HER2-positive metastatic breast cancer: pivotal trials. Oncol 2001; 61(suppl 2): 14–21 The recent guideline publication in the Journal of Clinical Pathology gives a very comprehensive overview of current recommendations for HER2 testing in the UK. Reference: • Walker RA et al. HER2 testing in the UK: further update to recommendations. J Clin Pathol 2008; 61: 818–824 Patients eligible for trastuzumab are those with IHC3+ OR ISH positive tumours.	
SH	Roche Products Limited	177.3	Full	60	21-23	*'Trastuzumab treatment beyond progression is not recommended unless the site of progression is within the CNS.'* Roche would like to highlight the following data in relation to this statement demonstrating both preclinical and clinical efficacy of trastuzumab in	Trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data. We encourage Roche to provide this data for review.

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						multiple lines of therapy: Preclinical data indicate (Pietras et al 1998; 17: 2235-2249) that Trastuzumab is effective against tumour cell proliferation for as long as it is present - if Trastuzumab is withdrawn rapid tumour cell regrowth occurs. There are a lack of clinical data with sound statistics on trastuzumab resistance, potential mechanisms have been studied in vitro but cannot be extrapolated to the clinical setting References: • Barok M, et al. Mol Cancer Ther 2007;6:2065–72. Barok M, et al. Cancer Lett 2008;260:198–208, Nahta R & Esteva F. Breast Cancer Res 2006;8:215. Antibody-dependent cellular-cytotoxicity (ADCC) and inhibition of HER2-mediated signalling have been demonstrated as major mechanisms of action of Trastuzumab in preclinical models and in vivo. Reference: • Nahta R & Esteva F Breast Cancer Res 2006;8:215 Pre-clinical data supports the hypothesis that cells still retain sensitivity to the chemotherapy-potentiating effects of trastuzumab and that continued administration of trastuzumab with a different second-line chemotherapy agent may result in a better clinical outcome than using the chemotherapy agent alone. Biological agents such as trastuzumab may also have benefits over chemotherapy agents in the long term treatment of metastatic breast cancer as cumulative toxicity has not been demonstrated.	

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						References: • Fujimoto-Ouchi. K et al. Preclinical study of continuous administration of trastuzumab as combination therapy after disease progression with trastuzumab monotherapy. Proc. Am. Soc. Clin Oncol 2005; 23, Abs 5062 • Shirane M et al. Preclinical study of continuous administration of trastuzumab as combination therapy after disease progression with trastuzumab monotherapy. European journal of cancer, supplement 2005; 3: 115 • Bell R. Review paper. Duration of therapy in metastatic breast cancer: management using Trastuzumab. Anti-cancer Drugs 2001; 12: 561–568 A wealth of retrospective analyses, a single arm prospective trial (Bartsch 2007) and a randomised clinical trial (von Minckwitz 2008) all provide consistent results demonstrating that continuation of Trastuzumab beyond progression (in combination with a change of chemotherapy agent) extends survival compared with stopping Trastuzumab on progression. Supporting references are as follows: • Von Minckwitz G et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER-2 positive metastatic breast cancer progressing during trastuzumab treatment – the TBP phase III study (GBG 26 / BIG 3-05). 44th American Society of Clinical Oncology annual meeting 2008; Poster. www.asco.org	

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						• Extra JM et al. Favourable effect of continued trastuzumab treatment in metastatic breast cancer patients: results from the French Hermine cohort study. San Antonio Breast Cancer Symposium 2006; Abs 2064. www.sabcs.org • Jackisch C et al. Routine clinical usage of trastuzumab (Trastuzumab®) in advanced breast cancer in Germany from 2001 to 2006. San Antonio Breast Cancer Symposium 2007: Poster 2134 • Menard S. Observational Demetra study: Survival of metastatic breast carcinoma patients after treatment with trastuzumab. J Clin Oncol 2008; 26: Abstract 1062 • Bartsch R et al. Capecitabine and trastuzumab in heavily pretreated patients with metastatic breast cancer. J Clin Oncol published ahead of print 6th August 2007 Bartsch 2007 JCO was a prospective single-arm study (n=40) in which patients with HER2+ MBC were treated with Trastuzumab plus Xeloda to disease progression or unacceptable toxicity. Previous treatment must have included adjuvant or palliative anthracycline and taxane or vinorelbine and a minimum of one previous line of Trastuzumab-containing therapy for HER2+ metastatic disease. After a median follow-up of 19 months, median TTP was 8 months and OS 24 months. In addition, 6 patients (15%) with pre-existing cerebral lesions were included in the study, 3 (50%) of which gained clinical benefit from XH therapy. Although this was a single arm study, the outcomes	

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						are consistent with the data presented from the randomised GBG26 trial described below. Results from the GBG26 study were presented by von Minckwitz et al at ASCO 2008 (Abstract 1025). Patients who had progressed on Trastuzumab-based first-line therapy (plus taxane or non-taxane chemotherapy) or Trastuzumab monotherapy were randomised to either continue Trastuzumab in combination with Xeloda or stop Trastuzumab treatment and receive Xeloda monotherapy. The trial planned to recruit 241 patients per arm but was stopped early, in May 2007, after recruitment of 78 patients per arm. There were two main reasons: • FDA registration of lapatinib for Trastuzumab progressors • Slow accrual due to unwillingness of HER2+ patients to enter the Xeloda monotherapy arm Despite the reduced numbers, the study demonstrated a significant 46% (3 month) improvement in TTP (from 5.6 to 8.2 months HR=0.69: 2-sided p=0.034; 1-sided p=0.015) and 5 month (25%) improvement in OS (from 20.4 to 25.5 months, HR 0.76; P value: 2-sided p=0.26; 1-sided p=0.13) for patients who continued Trastuzumab beyond progression versus those who stopped Trastuzumab on progression. There were no unexpected toxicities with the combination of Trastuzumab plus Xeloda. During therapy, only 1 patient had an LVEF decrease to <40 and 2.9% (n=2) of patients receiving Xeloda and 4.9% (n=3) receiving Trastuzumab plus Xeloda had other severe cardiac events. Importantly, there were no therapy-related deaths in the study. The study was originally designed with 80% power to	

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						detect 27.5% improvement in TTP from 4 to 5.1 months for continuing Trastuzumab beyond progression. Although the trial only recruited 32% patients (78 per arm) it actually showed a 46% improvement in TTP from 5.6 (X) to 8.2 (XH) months (a greater difference than the study was powered to show), demonstrating the magnitude of benefit of continuing Trastuzumab beyond progression in combination with Xeloda compared to stopping Trastuzumab on progression. Having fewer patients than planned does not invalidate a significant result. Based on the evidence base summarised above from both retrospective and prospective studies investigating the benefit of continuing trastuzumab beyond progression, Trastuzumab should be continued irrespective of site of progression (CNS or visceral).	
SH	Roche Products Limited	177.30	Full	60	22; 35-42	As previously mentioned, trastuzumab treatment beyond progression is not recommended unless the site of progression is within the CNS. We would draw your attention to the following data showing efficacy of trastuzumab in multiple lines of therapy: • Von Minckwitz G et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER-2 positive metastatic breast cancer progressing during trastuzumab treatment – the TBP phase III study (GBG 26 / BIG 3-05). 44th American Society of Clinical Oncology annual meeting 2008; Poster. www.asco.org • Von Minckwitz G et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER-2 positive metastatic breast cancer progressing during trastuzumab treatment – the TBP phase III study (GBG 26 / BIG 3-05). European Society of Medical Oncology	Trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data. We encourage Roche to provide this data for review.

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						2008; Presentation. • Chollet P et al. Clinical benefit with trastuzumab plus vinorelbine beyond disease progression in women with HER2-positive metastatic breast cancer. American Society of Clinical Oncology Breast Cancer Symposium 2007; Abs 243. www.asco.org • Tripathy D et al. Safety of treatment of metastatic breast cancer with trastuzumab beyond disease progression. J Clin Oncol 2004; 22(6): 1063–1070 • Bartsch R et al. Capecitabine and trastuzumab in heavily pretreated patients with metastatic breast cancer. J Clin Oncol published ahead of print 6th August 2007 • Bartsch R et al. Analysis of trastuzumab and chemotherapy in advanced breast cancer after the failure of at least one earlier combination: An observational study. BMC Cancer 2006; 6: 63 (doi:10.1186/1471-2407-6-63) • Extra JM et al. Favourable effect of continued trastuzumab treatment in metastatic breast cancer patients: results from the French Hermine cohort study. San Antonio Breast Cancer Symposium 2006; Abs 2064. www.sabcs.org • Mackey J, et al. Continued use of Trastuzumab after disease progression in women with HER2-positive (HER2+) metastatic breast cancer (MBC): results from a retrospective analysis of 105 cases. Proc Am Soc Clin Oncol 2002; Abs 207	

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						• Gelmon KA et al. Use of trastuzumab beyond disease progression: observations from a retrospective review of case histories. Clin Breast Cancer 2004; 5(1): 52–58 • Fountzilas G et al. Continuation of trastuzumab beyond disease progression is feasible and safe in patients with metastatic breast cancer: a retrospective analysis of 80 cases by the Hellenic cooperative oncology group. Clin Breast Cancer 2003; 4(2): 120–125 • Razis E, et al. Commentary. Continuation of trastuzumab beyond disease progression: more questions than answers. Clin Breast Cancer 2004; 5(1): 59–62 • Stemmler HJ et al. Prolonged survival of patients receiving trastuzumab beyond disease progression for HER2 overexpressing metastatic breast cancer (MBC). Onkologie 2005; 28: 582–586 • Garcia-Saenz J et al. Trastuzumab associated with successive cytotoxic therapies beyond disease progression in metastatic breast cancer. Proc Am Soc Clin Oncol 2006; Abs 10617 • Montemurro F et al. Continuation of trastuzumab beyond disease progression. Journal of clinical oncology 2005; 23: 2866-8 • Del Bianco S and Rondinelli R. Trastuzumab-containing therapies: Activity beyond disease progression in M.B.C.--A pivotal experience. Proc Am Soc Clin Oncol	

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						2006; Abs 10788 • Tokajuk P et al. Activity of trastuzumab-based therapy beyond disease progression in heavily pretreated metastatic breast cancer patients - single institution experience. Proc Am Soc Clin Oncol 2006; Abs 13159 • Adamo V et al. Safety and activity of trastuzumab-containing therapies for the treatment of metastatic breast cancer: our long-term clinical experience (GOIM study). Annals of Oncology 2007; 18 (Supplement 6): vi11–vi15	
SH	Roche Products Limited	177.31	Full	61	2	"A very recent, unpublished RCT showed that TRZ improved the esecond line capecitabine in Her2 +ve patients with metastatic diseashad previously received TRZ in the adjuvant or first line setting." It is unclear currently as to which study this statement refers. roche recommendeds a more clear reference to the publication would be helpful.	The appropriate reference citation was inserted into the text however we have amended the text to make it clearer.

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SH	Roche Products Limited	177.32	Full	61	9-14	The need for further research on the use of trastuzumab beyond progression is stated. We would draw your attention to the following published data: The GBG-26 TBP (MO17038) study is a phase III randomised multi-centre trial which was designed to assess time to progression in patients who received capecitabine alone or in combination with trastuzumab in patients with pathologically confirmed HER2 positive MBC and who had received prior trastuzumab therapy. An interim report of the GBG-26 study was presented at the San Antonio Breast Cancer Symposium (SABCS) in 2007. Eligible patients were allowed no more than one chemotherapy for palliation, had to have an LVEF of ≥50%, and had to have had a trastuzumab-free treatment interval of more than six weeks. The primary end point of the trial was TTP. Secondary end points were ORR, duration of response, clinical benefit (CR, PR or SD for more than 24 weeks), progression-free survival (PFS), (OS) and safety of the capecitabine/trastuzumab combination therapy. The authors stated that treatment with trastuzumab and capecitabine beyond progression exhibited numerically fewer events of tumour progression (48 vs. 53 in the capecitabine alone arm) and deaths (26 vs. 31). Trastuzumab and capecitabine combination therapy reached a response rate of 48.9%, whereas capecitabine monotherapy reached a rate of 24.6%. The authors also stated that the combination therapy was a feasible schedule without unexpected severe toxicities, especially without long-term cardiac toxicity. Further results of GBG-26 were presented at the American Society of Clinical Oncology (ASCO)	The reported studies are small. The GBG-26 study has yet to demonstrate a statistically significant improvement in overall survival. Cost-effectiveness data from these studies has yet to be made available. At this point it is not possible to know if the data that will be made available from these studies will be adequate to perform good quality cost-effectiveness analysis. Trastuzumab is an extremely high cost treatment and it would be inappropriate for patterns of use to change until adequate research demonstrating its cost effectiveness has been performed. We have amended these research recommendations to include collection of data required for prospective cost effectiveness analysis.

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						conference in 2008. The authors stated that no increase in toxicity was observed in patients receiving trastuzumab and capecitabine in combination. They concluded that continuing trastuzumab beyond progression improved efficacy of second line capecitabine therapy in HER2 positive MBC patients. Further tolerability results from GBG-26 were presented at the European Society of Medical Oncology (ESMO) conference in 2008. The results showed that tolerability of capecitabine did not change with continuation of trastuzumab treatment. Grade 1/2 anemia was observed more often in the combination arm than in the capecitabine-alone arm (64.0% vs. 41.6%, p=0.02). One patient in the capecitabine plus trastuzumab arm experienced a decrease in left ventricular function of <40. No therapy-related deaths were observed. The authors concluded that there was no increase in toxicity in the trastuzumab plus capecitabine combination arm of the study. Data have been published from the Hermine study, an observational French cohort study by 102 oncologists of a large patient population treated with trastuzumab-based therapy under real-life conditions. After a minimum follow up of two years, data analysis from the Hermine study was performed comparing patients treated in the first-line setting who continued trastuzumab with those who discontinued trastuzumab-based treatment at disease progression. A total of 221 evaluable patients received trastuzumab as first-line treatment, of whom 184 progressed or died during the follow up period. Among the 177 patients who progressed, trastuzumab was continued in 60% (n=107, Group A) and discontinued before or at progression in 40% (n=70, Group B). Median duration of trastuzumab	

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						treatment prior to progression was 10.2 months in Group A and 6.1 months in Group B. Total treatment duration was 27.4 months in Group A and median TTP was longer in Group A compared with Group B (10.2 vs. 7.1 months respectively). Median OS was 16.8 months (95% CI: 12.5-19.5) for Group B and had not yet been reached at 27.8 months follow-up for Group A, indicating a significant survival benefit in this patient group (p<0.0001). OS at 2 years was 73.7% in Group A compared with 24.7% in Group B.	
SH	Roche Products Limited	177.4	Full	61	10-12	*Recommendation for an RCT of trastuzumab beyond progression* Currently, large clinical studies in the HER2+ MBC setting are hard to justify in terms of available patient numbers. As detailed above, evidence from a randomised controlled trial - GBG26, a prospective single arm study and a wealth of retrospective studies - all provide consistent results demonstrating that the continuation of trastuzumab beyond progression (in combination with chemotherapy) extends survival (by up to 30 months, Demetra ASCO 2008) compared with stopping trastuzumab upon disease progression.	The reported studies are small. The GBG-26 study has yet to demonstrate a statistically significant improvement in overall survival. Cost-effectiveness data from these studies has yet to be made available. At this point it is not possible to know if the data that will be made available from these studies will be adequate to perform good quality cost-effectiveness analysis. Trastuzumab is an extremely high cost treatment and it would be inappropriate for patterns of use to change until adequate research demonstrating its cost effectiveness has been performed.

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						References: • Von Minckwitz G et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER-2 positive metastatic breast cancer progressing during trastuzumab treatment – the TBP phase III study (GBG 26 / BIG 3-05). 44th American Society of Clinical Oncology annual meeting 2008; Poster. www.asco.org • Von Minckwitz G et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER-2 positive metastatic breast cancer progressing during trastuzumab treatment – the TBP phase III study (GBG 26 / BIG 3-05). European Society of Medical Oncology 2008; Presentation. • Extra JM et al. Favourable effect of continued trastuzumab treatment in metastatic breast cancer patients: results from the French Hermine cohort study. San Antonio Breast Cancer Symposium 2006; Abs 2064. www.sabcs.org • Jackisch C et al. Routine clinical usage of trastuzumab (Trastuzumab®) in advanced breast cancer in Germany from 2001 to 2006. San Antonio Breast Cancer Symposium 2007: Poster 2134 • Menard S. Observational Demetra study: Survival of metastatic breast carcinoma patients after treatment with trastuzumab. J Clin Oncol 2008; 26: Abstract 1062 • Bartsch R et al. Capecitabine and	We have amended these research recommendations to include collection of data required for prospective cost effectiveness analysis.

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						trastuzumab in heavily pretreated patients with metastatic breast cancer. J Clin Oncol published ahead of print 6th August 2007	
SH	Roche Products Limited	177.5	Full	61	12-14	*Treatment with Trastuzumab at relapse* Roche strongly believe that patients who have received adjuvant Trastuzumab should still be eligible to receive Trastuzumab in the 1st line metastatic setting should they relapse. The recommendation for an RCT of trastuzumab in this setting is hard to justify: such a study would recruit extremely slowly due to low numbers of available patients and could also be problematic in terms of patient acceptance. Trastuzumab has multiple modes of action, including activation of the immune system via ADCC (Nahta R & Esteva F Breast Cancer Res 2006;8:215). Due to this unique mode of action, patients who respond to trastuzumab the first time are more likely to respond a second time. (Nahta R, Esteva FJ. Trastuzumab: mechanisms of action and resistance. Cancer Letters 2006; 232: 123-138). An RCT of Trastuzumab in this setting is already underway, with initial data having been presented. RHEA (WO17299) is an ongoing open-label, multicentre, phase II study which is investigating the efficacy and safety of trastuzumab in first-line HER2 positive metastatic breast cancer in patients who have relapsed after neoadjuvant or adjuvant trastuzumab. The primary end point is overall response rate and the primary outcomes are tumour response rate and progression. Secondary outcomes are duration of response, progression-free survival,	Adequate evidence of clinical and cost-effectiveness should be provided to justify the use of a high-cost intervention such as this. At a minimum this should include evidence of increased clinical effectiveness in comparison with no trastuzumab from an appropriately powered RCT, together with robust cost effectiveness data. We do not believe that that data you have listed below provides this and therefore feel that our research recommendation is still appropriate.

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						time to treatment failure, clinical benefit rate and survival. Eligible patients will have received at least 10 months of trastuzumab treatment for HER2 positive early breast cancer and will have relapsed 12 months or more after completing adjuvant trastuzumab. Patients are being randomised into two arms of the study. Patients in arm 1 will receive trastuzumab monotherapy (4 mg/kg loading dose followed by 2 mg/kg maintenance dose weekly). Patients in arm 2 will receive trastuzumab (4 mg/kg loading dose then 2 mg/kg maintenance dose weekly), with docetaxel (100 mg/m2 every three weeks for six cycles) or with paclitaxel (175 mg/m2 every three weeks for six cycles or 75 mg/m2 every week for 18 cycles). The planned cohort size is 40 patients in each arm of the study. Bell et al reported preliminary efficacy data at the American Society of Clinical Oncology (ASCO) conference in 2007. 10 patients had been enrolled in arm 2 of the study and nine of these patients had undergone one or more post-baseline tumour assessment. Of these, partial responses were observed in four patients (duration of response (4.2 to 12 months) and stable disease was observed in a further four patients. Seven patients continued to receive treatment. The authors stated that this continuation of treatment suggested durable benefit of trastuzumab in combination with taxane therapy. They also stated that the pre-defined early-stopping rule for arm 2 had been surpassed as more than three responses have been observed, and that the preliminary data suggest that trastuzumab can be effective after recurrence of disease following adjuvant use. Recruitment into both arms of the trial is ongoing.	

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						Results of the study are due to be presented in 2010. References: • A Study of Trastuzumab (Trastuzumab) in Women With Metastatic Breast Cancer. US National Institutes of Health. http://www.clinicaltrials.gov/ct2/show/NCT00475670?term=WO17299&rank=1. Accessed: 4th September 2008 • Bell R et al. Trastuzumab re-treatment in patients who relapse following adjuvant trastuzumab therapy: preliminary efficiacy data from the RHEA trial. American Society of Clinical Oncology 2007. Abstract 245. www.asco.org Other supportive data for multiple responses to trastuzumab are those showing efficacy in treatment beyond progression. Repeated and sustained responses occur in this group as proof of subsequent response, but with appropriate caveats, as the only data in this setting currently available are from the RHEA study. Data have been published from the Hermine study, an observational French cohort study by 102 oncologists of a large patient population treated with trastuzumab-based therapy under real-life conditions. After a minimum follow up of two years, data analysis from the Hermine study was performed comparing patients treated in the first-line setting who continued trastuzumab with those who discontinued trastuzumab-based treatment at disease progression. A total of 221 evaluable patients received trastuzumab as first-line treatment, of whom 184 progressed or died during the follow up period.	

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						Among the 177 patients who progressed, trastuzumab was continued in 60% (n=107, Group A) and discontinued before or at progression in 40% (n=70, Group B). Median duration of trastuzumab treatment prior to progression was 10.2 months in Group A and 6.1 months in Group B. Total treatment duration was 27.4 months in Group A and median TTP was longer in Group A compared with Group B (10.2 vs. 7.1 months respectively). Median OS was 16.8 months (95% CI: 12.5-19.5) for Group B and had not yet been reached at 27.8 months follow-up for Group A, indicating a significant survival benefit in this patient group ($p<0.0001$). OS at 2 years was 73.7% in Group A compared with 24.7% in Group B. Based on the above results, the authors concluded that continued trastuzumab treatment after disease progression in women with HER2-positive MBC appears to be associated with a marked survival advantage. Reference: • Extra JM et al. Favourable effect of continued trastuzumab treatment in metastatic breast cancer patients: results from the French Hermine cohort study. San Antonio Breast Cancer Symposium 2006; Abs 2064. www.sabcs.org Pre-clinical data also supports the hypothesis that cells still retain sensitivity to the chemotherapy potentiating effects of trastuzumab and that therefore, continued administration of trastuzumab with a different, second-line chemotherapy agent may result in a better clinical outcome than using the chemotherapy agent alone. Biological agents such as trastuzumab may also have benefits over chemotherapy agents in the long term treatment of	

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						metastatic breast cancer as cumulative toxicity has not been demonstrated. References: • Fujimoto-Ouchi. K et al. Preclinical study of continuous administration of trastuzumab as combination therapy after disease progression with trastuzumab monotherapy. Proc. Am. Soc. Clin Oncol 2005; 23, Abs 5062 • Shirane M et al. Preclinical study of continuous administration of trastuzumab as combination therapy after disease progression with trastuzumab monotherapy. European journal of cancer, supplement 2005; 3: 115 • Bell R. Review paper. Duration of therapy in metastatic breast cancer: management using Trastuzumab. Anti-cancer Drugs 2001; 12: 561–568 Furthermore, NICE assumed all patients would be retreated in the metastatic setting following adjuvant Trastuzumab in the analysis of the clinical and cost-effectiveness of adjuvant Trastuzumab (TA107). Under this assumption, adjuvant Trastuzumab continued to be highly cost effective, with an ICER of £18,000 per QALY gained. In summary Roche can not see any valid clinical argument that the response to trastuzumab in the first line metastatic setting would in any way be compromised by virtue of a patient already having received trastuzumab in the adjuvant setting. Previous NICE technology appraisals (rituximab for relapsed follicular lymphoma) permitted the re-	

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						treatment of rituximab in combination with chemotherapy for second line patients even if rituximab had been administered in the first line setting. It is important to note that the use of Taxanes in the metastatic setting is not conditional on whether a patient has or has not been administered in the adjuvant setting. Considering the available clinical evidence base, this appears an unreasonable inconsistency and inequality within the current guideline. This recommendation occurred despite the fact the clinical trial did not include rituximab experienced patients. In this example the lack of evidence or clinical rational to suggest why the efficacy results would be compromised by prior treatment with rituximab (also a monoclonal antibody) was considered sufficient evidence to permit a re-treatment recommendation.	
SH	Roche Products Limited	177.6	Full	21	2-3	Endocrine Therapy Algorithm – ER+/HER2+ Tumours RCT data from the TanDem study indicate improved response rates and duration of response in HER2 positive tumours if trastuzumab is added in to endocrine therapy. The endocrine treatment algorithm already includes the option to add in chemotherapy if a rapid response is required. It should also include the option to add in trastuzumab for the inevitably high-risk HER2 positive tumours. The best responses to trastuzumab are seen in the first line setting. This does not take into account the value of adding trastuzumab to an aromatase inhibitor in ER+/HER2+	Trastuzumab in combination with AIs is on the list of topics being considered by the NICE Topic Selection Panel for Cancer as a future STA. We have therefore not investigated this combination within the guideline.

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						(co-positive) tumours. Approximately, 50% of HER2+ breast cancers are also ER+. Evidence suggests HER2 overexpression is associated with resistance to hormone therapy (ref Jones 2003, Johnston 2007, Orman 2007) due to crosstalk between HER2 and ER signalling pathways (Osborne CK Clin Cancer Res 2001; 7 (Suppl);4338s-4342s; Dowsett Endocrin Relat Cancer 2001; 8:191-195) The Tandem study (Tandem, Kaufman B, et al ESMO 2006 Abstract LBA2; Mackey et al SABCS 2006, Abs 3) randomised postmenopausal women with HER2+ and ER+ breast cancer to receive either anastrozole alone or anastrozole in combination with Trastuzumab as first-line treatment for MBC. The primary endpoint was progression-free survival (PFS). The addition of Trastuzumab to anastrozole significantly improved PFS from 2.4 to 4.8 months (HR 0.63; p=0.0016) for women with HER2 and HR co-positive MBC. Furthermore, overall response rate tripled (from 6.8% to 20.3%; p=0.018) and clinical benefit rate increased by 53% (27.9% to 42.7%; p=0.026) with addition of Trastuzumab to anastrozole compared with anastrozole alone. Despite 70% of patients who progressed on anastrozole alone receiving Trastuzumab after progression, there was a 4.6 month improvement in overall survival (23.9 to 28.5; p 0.325). In addition, a post hoc analysis indicated a median OS benefit of 11.3 months for patients who received anastrozole plus Trastuzumab (n=103) vs anastrozole alone and did not cross over to receive Trastuzumab at disease	

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						progression (n=31) (28.5 vs 17.2 months, p=0.0479) There were no new or unexpected Aes associated with the addition of Trastuzumab to anastrozole. The results of the Tandem trial demonstrate that the combination of Trastuzumab plus anastrozole significantly improves PFS, ORR, CBR, and may prolong OS compared with anastrozole alone in women with HER2 and HR co-positive MBC. This suggests that simultaneous targeting of both pathways improves outcomes over hormone therapy alone in co-positive MBC. At the end of the algorithm chemotherapy should be included as an option for endocrine-resistant patients.	We have made this change.
SH	Roche Products Limited	177.7	Full	22	2-3	Chemotherapy algorithm Generalisation and simplification of treatment pathways in this way is very difficult, various groups of patients with different treatment histories need to be taken into account when developing the algorithm. While the algorithm adequately encompasses tumour biology it does not take into account various patient factors which are important when making treatment selections – such as biological age, performance status, and organ function. Roche considers that the algorithm currently oversimplifies the treatment decisions in metastatic breast cancer. For example, it does not identify patients who have received : A) a taxane (docetaxel) in the adjuvant setting. B) both an anthracycline and a taxane in the	These algorithms are intended to be a pictorial overview of the recommendations in the guideline not a substitute for them. Since both algorithms and recommendations are intended to be read together, some detail has been removed from the algorithms to make them easier to understand. This document is a guideline and not a mandatory approach to clinical practice. As such it does not replace clinical judgement. The GDG has made no recommendations for this specific situation. This will be a matter for clinical judgement.

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						adjuvant setting. Pre-treatment with these agents will affect the decisions made in mBC; If the maximum dose of anthracycline has been received in the adjuvant setting then either taxane monotherapy or a combination such as docetaxel/capecitabine (XT) should be considered, particularly in a younger patient with good performance status (as recommended in NICE Technology Appraisal 62, May 2003). Performance status/age of the patient has not been taken into account in the 1st line therapy recommendations. A very frail, elderly patient would not be given docetaxel monotherapy; and would probably have a better treatment experience with capecitabine monotherapy. A younger fitter patient could tolerate a more difficult regimen such as XT. Should a patient have received both an anthracycline and docetaxel in the adjuvant setting, then 1st line capecitabine monotherapy is a widely-used and efficacious regimen. This needs to be captured in the algorithm. A number of studies have investigated the use of capecitabine as first-line therapy in anthracycline and taxane pretreated/unsuitable patients. In one key first-line trial by Stockler et al. patients unsuited to more intensive chemotherapy were randomised to one of three arms: intermittent Xeloda (1,000 mg/m2, twice daily days 1-14, every 3 weeks), continuous Xeloda (650 mg/m2 twice daily, days 1-21, every 3 weeks) or classical (oral) CMF. Xeloda (combined intermittent and continuous arms) gave a statistically significant overall survival	This guideline was tasked with updating technology appraisal 62. As such the recommendations from TA 62 have been replaced by the recommendations in this guideline. The GDG has recommended that combination chemotherapy be considered for 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.

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						benefit over CMF. PFS and RR were similar in the two arms – the investigators attribute the survival benefit to the considerably longer duration of treatment and associated disease control in the Xeloda arm. Reference: • Stockler MR et al. A randomized trial of capecitabine I given intermittently (IC) rather than continuously (CC) compared to classical CMF as first-line chemotherapy for advanced breast cancer (ABC).J Clin Oncol 2007; 25(18S):1031. Bajetta et al. assessed the efficacy and safety of first/second-line capecitabine in 73 advanced/metastatic breast cancer patients aged 65 years (for 84% of patients capecitabine was given as first-line chemotherapy). The first 30 patients received Xeloda 1250 mg/m2 twice daily, days 1–14, every 3 weeks. This was subsequently reduced to 1000 mg/m2 for the next 43 patients following the occurrence of 2 diarrhoea-related deaths. In this patient cohort, capecitabine showed considerable activity achieving a high clinical benefit rate (CR/PR + SD ≥24 weeks). No significant differences in clinical benefit rates and time to progression were observed between the lower and higher dose groups The authors conclude that capecitabine 1000 mg/m2 twice daily, days 1–14, every 3 weeks is a 'safe' and 'effective' treatment for patients ³65 years with locally advanced/metastatic breast cancer.. Reference: • Bajetta E et al. Safety and efficacy of two	

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						different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 2005; 23: 2155–61. O'Shaughnessy et al. randomised 95 patients with advanced and/or metastatic breast cancer to receive either capecitabine or CMF as first-line treatment. Patients in the capecitabine arm received capecitabine 1255 mg/m2 twice daily days 1-14, every 3 weeks. Patients in the CMF arm received: cyclophosphamide 600 mg/m2, methotrexate 40 mg/m2 and 5-FU 600 mg/m2 intravenously once every 3 weeks. The primary objective was to define the investigator-assessed objective response rate produced with intermittent capecitabine as first-line treatment of older metastatic breast cancer patients. This trial was not designed to detect a statistical difference between capecitabine and CMF, but to evaluate the objective response rate for each of the two treatment regimens using CMF as a reference arm to diminish any bias in the patient recruitment. There were no major efficacy differences between capecitabine and CMF. Despite the safety profiles of both treatments being different, the majority of treatment-related adverse events were mild/moderate. Reference: • O'Shaughnessy J et al. Randomized, open-label, phase II trial of oral capecitabine (Xeloda®) vs. a reference arm of intravenous CMF (cyclophosphamide,	

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						methotrexate and 5-fluorouraeil) as first-line therapy for advanced/metastatic breast cancer. Ann Oncol 2001;12:1247–54.	
SH	Roche Products Limited	177.8	Full	22	2-3	Chemotherapy Algorithm – Retreatment with trastuzumab at relapse As previously stated, the chemotherapy algorithm differentiates between those HER2+ patients who are trastuzumab I and those who received it in the adjuvant setting. The algorithm states that further research is required for the latter group. As more and more therapies for breast cancer are extended into the adjuvant setting, less data will become available for their subsequent use in those patients who suffer a relapse. An example would be the use of docetaxel in first line treatment. Increasing amounts of docetaxel are being used adjuvantly, there is no data on retreatment in this setting. Trastuzumab has multiple modes of action, including activation of the immune system via ADCC (Nahta R & Esteva F Breast Cancer Res 2006;8:215), and as a monoclonal antibody, trastuzumab is not subject to the resistance mechanisms demonstrated by cytotoxic drugs. It's mode of action encompasses not only direct 'blocking' of the HER2 receptor on the tumour cell, there is also an anti-angiogenic component, and antibody dependant cellular cytotoxicity (ADCC) – recruiting the patient's immune system to act against the tumour. References: • Nahta R, Esteva FJ. Trastuzumab:	Adequate evidence of clinical and cost-effectiveness needs to be provided to justify the use of a high cost intervention such as this. At a minimum this should include evidence of increased clinical effectiveness in comparison with no trastuzumab from an appropriately powered RCT, together with robust cost effectiveness data.

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						mechanisms of action and resistance. Cancer Letters 2006; 232: 123-138 Because of this, in common with other monoclonal antibodies multiple responses to rechallenge with Trastuzumab are common in clinical practice. Pre-clinical data also supports the hypothesis that cells still retain sensitivity to the chemotherapy potentiating effects of trastuzumab and that therefore, continued administration of trastuzumab with a different, second-line chemotherapy agent may result in a better clinical outcome than using the chemotherapy agent alone. Biological agents such as trastuzumab may also have benefits over chemotherapy agents in the long term treatment of metastatic breast cancer as cumulative toxicity has not been demonstrated. References: • Fujimoto-Ouchi. K et al. Preclinical study of continuous administration of trastuzumab as combination therapy after disease progression with trastuzumab monotherapy. Proc. Am. Soc. Clin Oncol 2005; 23, Abs 5062 • Shirane M et al. Preclinical study of continuous administration of trastuzumab as combination therapy after disease progression with trastuzumab monotherapy. European journal of cancer, supplement 2005; 3: 115 • Bell R. Review paper. Duration of therapy in metastatic breast cancer: management using Trastuzumab. Anti-cancer Drugs 2001; 12: 561–568	

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						An RCT of Trastuzumab in this retreatment setting is already underway, with initial data having been presented. RHEA (WO17299) is an ongoing open-label, multicentre, phase II study which is investigating the efficacy and safety of trastuzumab in first-line HER2 positive metastatic breast cancer in patients who have relapsed after neoadjuvant or adjuvant trastuzumab. The primary end point is overall response rate and the primary outcomes are tumour response rate and progression. Secondary outcomes are duration of response, progression-free survival, time to treatment failure, clinical benefit rate and survival. Eligible patients will have received at least 10 months of trastuzumab treatment for HER2 positive early breast cancer and will have relapsed 12 months or more after completing adjuvant trastuzumab. Patients are being randomised into two arms of the study. Patients in arm 1 will receive trastuzumab monotherapy (4 mg/kg loading dose followed by 2 mg/kg maintenance dose weekly). Patients in arm 2 will receive trastuzumab (4 mg/kg loading dose then 2 mg/kg maintenance dose weekly), with docetaxel (100 mg/m2 every three weeks for six cycles) or with paclitaxel (175 mg/m2 every three weeks for six cycles or 75 mg/m2 every week for 18 cycles). The planned cohort size is 40 patients in each arm of the study. Bell et al reported preliminary efficacy data at the American Society of Clinical Oncology (ASCO) conference in 2007. 10 patients had been enrolled in arm 2 of the study and nine of these patients had undergone one or more post-baseline tumour assessment. Of these, partial responses were observed in four patients (duration of response (4.2 to	

Type	Stakeholder	Order No	Document	Page No	Line No	Comments Please insert each new comment in a new row.	Developer's Response Please respond to each comment
						12 months) and stable disease was observed in a further four patients. Seven patients continued to receive treatment. The authors stated that this continuation of treatment suggested durable benefit of trastuzumab in combination with taxane therapy. They also stated that the pre-defined early-stopping rule for arm 2 had been surpassed as more than three responses have been observed, and that the preliminary data suggest that trastuzumab can be effective after recurrence of disease following adjuvant use. Recruitment into both arms of the trial is ongoing. Results of the study are due to be presented in 2010. References: • A Study of Trastuzumab (Trastuzumab) in Women With Metastatic Breast Cancer. US National Institutes of Health. http://www.clinicaltrials.gov/ct2/show/NCT00475670?term=WO17299&rank=1. Accessed: 4th September 2008 • Bell R et al. Trastuzumab re-treatment in patients who relapse following adjuvant trastuzumab therapy: preliminary efficiacy data from the RHEA trial. American Society of Clinical Oncology 2007. Abstract 245. www.asco.org Other supportive data for multiple responses to trastuzumab are those showing efficacy in treatment beyond progression in metastatic disease. Repeated and sustained responses occur in this group as proof of subsequent response, but with appropriate caveats, as the only data in this setting currently	

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						available are from the RHEA study. Data have been published from the Hermine study, an observational French cohort study by 102 oncologists of a large patient population treated with trastuzumab-based therapy under real-life conditions. After a minimum follow up of two years, data analysis from the Hermine study was performed comparing patients treated in the first-line setting who continued trastuzumab with those who discontinued trastuzumab-based treatment at disease progression. A total of 221 evaluable patients received trastuzumab as first-line treatment, of whom 184 progressed or died during the follow up period. Among the 177 patients who progressed, trastuzumab was continued in 60% (n=107, Group A) and discontinued before or at progression in 40% (n=70, Group B). Median duration of trastuzumab treatment prior to progression was 10.2 months in Group A and 6.1 months in Group B. Total treatment duration was 27.4 months in Group A and median TTP was longer in Group A compared with Group B (10.2 vs. 7.1 months respectively). Median OS was 16.8 months (95% CI: 12.5-19.5) for Group B and had not yet been reached at 27.8 months follow-up for Group A, indicating a significant survival benefit in this patient group ($p<0.0001$). OS at 2 years was 73.7% in Group A compared with 24.7% in Group B. Based on the above results, the authors concluded that continued trastuzumab treatment after disease progression in women with HER2-positive MBC appears to be associated with a marked survival advantage. Reference:	

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						• Extra JM et al. Favourable effect of continued trastuzumab treatment in metastatic breast cancer patients: results from the French Hermine cohort study. San Antonio Breast Cancer Symposium 2006; Abs 2064. www.sabcs.org • O'Shaughnessy J et al. A randomized study of lapatinib alone or in combination with trastuzumab in heavily pretreated HER2+ metastatic breast cancer progressing on trastuzumab therapy. J Clin Oncol 2008; 26 (May 20 supplement): Abstract 1015 Furthermore, NICE assumed all patients would be retreated in the metastatic setting following adjuvant Trastuzumab in the analysis of the clinical and cost-effectiveness of adjuvant Trastuzumab (TA107). Despite this assumption, adjuvant Trastuzumab continued to be highly cost effective, with an ICER of £18,000 per QALY gained. The recommendation for an RCT of trastuzumab in this setting is hard to justify: such a study would recruit extremely slowly due to low numbers of available patients and would also be problematic in terms of patient acceptance of the observation arm. Patients who have received adjuvant Trastuzumab should be eligible to receive Trastuzumab in the 1st line metastatic setting should they relapse. Another important point for consideration – licenses for new therapies coming into the market will specify that they can only be used after failure of trastuzumab in the metastatic setting. If 1st line trastuzumab cannot be used in the increasing group of pre-treated patients, then subsequent therapy with other HER2 targeted agents will not be possible	

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						within the license of that agent. Finally, 'Research Required' suggests a lack of level 1 evidence. However real life patients with HER2 positive tumours do need to receive treatment when they relapse. Currently the best outcomes for these patients are achieved by the first line use of trastuzumab. Sometimes it is necessary to make a decision on a reasonable approach based upon the results in the small group of patients who take part in trials and extrapolate those to the patient in the clinic.	
SH	Rotherham Acute Trust	178				This organisation was approached but did not respond.	
SH	Rotherham Primary Care Trust	179				This organisation was approached but did not respond.	
SH	Royal Bolton Hospitals NHS Trust	180				This organisation was approached but did not respond.	
SH	Royal College of General Practitioners	181				This organisation was approached but did not respond.	
SH	Royal College of General Practitioners Wales	182				This organisation was approached but did not respond.	
SH	Royal College of Midwives	183				This organisation was approached but did not respond.	
SH	Royal College of Nursing	184	General			The RCN welcomes this guideline. It is comprehensive.	Thank you
SH	Royal College of Obstetricians and Gynaecologists	185				This organisation was approached but did not respond.	

SH	Royal College of Pathologists	186.0	General			If you have any comments about these two definitions of HER2 positive status, for the two breast cancer populations The definition of HER2 status positive in the early and locally advanced breast cancer guidelines, which is the same as that recommended in the most recent guidelines on HER2 testing in the UK, is the preferred definition, not the one taken from technology Appraisal 34.	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines.TA34 was published in 2002, and we acknowledge that the guidelines for HER2 testing have changed since that time. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	Royal College of Pathologists	186.1	Full	33	8-29	The recommendations that if ER and HER2 status are known from the primary tumour or that the primary tumour can be tested, there is no need for a further biopsy for assessment of ER/HER2 status is supported.	Thank you
SH	Royal College of Physicians London	187				SEE COMMENTS FROM NCRI (ORDER NO 128) JOINT RESPONSE	Thank you. Please see our responses to NCRI
SH	Royal College of Physicians/Royal College of Radiologists/Joint Council Clinical Oncology/ Association of Cancer Physicians	128.16	Full (1.3.2.2)	47	6-8	There is a meta-analysis which clearly shows superiority of ovarian suppression plus tamoxifen over tamoxifen alone in premenopausal women.	The GDG has not been able to identify a meta analysis comparing ovarian suppression plus tamoxifen with tamoxifen alone. The reference that you provided relates to a meta analysis showing superiority of ovarian suppression plus tamoxifen over ovarian suppression alone.
SH	Royal College of Psychiatrists	188				This organisation was approached but did not respond.	
SH	Royal College of Radiologists	189				SEE COMMENTS FROM NCRI (ORDER NO 128) JOINT RESPONSE	Thank you. Please see our responses to NCRI
SH	Royal College of Radiologists Breast Group	190				This organisation was approached but did not respond.	
SH	Royal College of Surgeons of England	243.0	Full	General		The College broadly welcome the direction and aim of the guidelines.	Thank you
SH	Royal College of Surgeons of England	243.1	Full	80	26	The guidelines on bone metastases do not reference the British Association of Surgical Oncology's guidelines on 'The Management of Metastatic Bone	This document is not a systematic review and as such was not appraised. We are not able to reference documents that have not been

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						Disease in the United Kingdom'. We would recommend these are included.	appraised.
SH	Royal Society of Medicine	191				This organisation was approached but did not respond.	
SH	Royal United Hospital Bath NHS Trust	192.0	FULL	45	20 +	Some reservation is expressed at the perceived somewhat dismissive attitude in the draft guidelines towards the value of tamoxifen in the treatment of advanced breast cancer. The guidelines draw attention to randomized trial evidence demonstrating the greater overall efficacy of 3rd generation aromatase inhibitors in post-menopausal women with advanced and metastatic cancer [either as first or second-line], and in particular the improved survival reported in one meta-analysis [but not another]. They draw attention also to the lack of evidence concerning optimal hormonal treatment after an aromatase inhibitor. However, there is a wealth of documentation concerning the efficacy of tamoxifen in advanced breast cancer and it may well retain a useful role. Prolonged disease control often depends on sequential usage of different hormonal treatments. It is arguable that there is more evidence for the use of an aromatase inhibitor after tamoxifen rather than the other way round, although we are not aware of evidence that prior aromatase inhibitor treatment renders tamoxifen less effective, other than through a general tendency for cancers to become less hormonally responsive as they are exposed to successive hormonal agents. Tamoxifen remains a reasonable relatively bone health preserving [and cheap] option for first-line use for selected patients who tolerate it well, particularly those with relatively indolent and non-visceral disease. It keeps open the option for aromatase inhibition later. It is worth pointing out that neither the	We do not feel that we have dismissed tamoxifen, we have based our recommendations on a systematic appraisal of the published evidence.

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						Ferretti 2006 meta-analysis nor the 2007 Cochrane review [Gibson et al] were able to demonstrate an overall survival advantage from first-line aromatase inhibitor usage, but the latter did demonstrate an overall survival advantage from second-line usage]. Aromatase inhibitors will undoubtedly be preferred as initial treatment for patients with visceral disease, but how strong is the evidence that patients with locally advanced [and relatively indolent] disease, and those with purely bone metastases, will be disadvantaged if treated initially with tamoxifen and monitored, and switched to an aromatase inhibitor as soon as treatment failure is evident? The guidelines are for 'advanced' breast cancer. The text seems to imply that 'advanced' and 'metastatic' are interchangeable, but some patients have inoperable but merely locally advanced disease. Might it not be helpful to define 'advanced' and for that matter 'metastatic'? In strict usage the latter embraces patients with merely nodal spread [and such an interpretation has allowed some patients in the past to receive herceptin probably outside the intent of the 2002 technology appraisal authors]. The guidelines also imply that tamoxifen is inappropriate for pre-menopausal patients if there has been prior exposure to tamoxifen as an adjuvant treatment. There will be some [admittedly a small number] pre-menopausal patients whose disease relapses some years after having completed adjuvant tamoxifen. How good is the evidence that they will not benefit from tamoxifen for their recurrent cancer?	A definition of "advanced breast cancer" is present in the glossary. We have added a definition of "metastatic breast cancer". Guidelines are intended to cover the majority of clinical situations, not all possible situations. We feel that the situation you describe would be unusual and therefore the guideline does not make recommendations on this. In unusual situations such as this we would expect clinical judgement to be used.
SH	Royal United Hospital Bath NHS Trust	192.1	FULL	96	10	The economic model would appear to assume that only capecitabine is an oral chemotherapeutic agent. Vinorelbine is of course also available for oral administration.	Yes, oral vinorelbine might be a suitable comparator. Unfortunately we did not find any clinical evidence of its effectiveness. As such it was not included in the economic model.

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SH	Royal West Sussex Trust	193				This organisation was approached but did not respond.	
SH	SACAR	194				This organisation was approached but did not respond.	
SH	Salford PCT	195				This organisation was approached but did not respond.	
SH	Sandwell PCT	196				This organisation was approached but did not respond.	
SH	Sanofi-Aventis	197.0	Full Guideline	General		The GDG has carried out a very thorough clinical review of the published literature on the diagnosis and treatment of advanced breast cancer. We are in general agreement with their findings and recommendations with just a few minor points which we wish to raise as detailed below. One general point is the lack of direct referencing to clinical trials to support specific statements. This would improve the document and its scientific transparency, allowing informed decisions to be made (see points 5 and 6 for specific examples).	Thank you Please see our responses to specific comments below.
SH	Sanofi-Aventis	197.10	Full	59	31-42	As stated in the Full guideline trastuzumab was approved by NICE in 2002. In February 2005, the institute proposed that its guidance on trastuzumab for advanced breast cancer (TA 34) be updated as part of the work on the upcoming breast cancer guideline and this was confirmed in May 2005. Given that the GDG was instructed by the institute to update TA 34 it seems surprising that they came to the conclusion in line 38 that '*the GDG could make no recommendation about the use of the combination of trastuzumab with docetaxel*'. In line 36 it states that this was '*due to the limited data available from the one published trial on this new combination*' as a result of which they determined that '*it was not possible to develop a robust health economic model*'.	The economic model used in TA34 was developed by Roche who would have had access to more data than would be available from published reports of the relevant trial. The GDG did not have access to an equivalent level of data when considering the combination of trastuzumab + docetaxel, and were therefore limited to using only data from the one published report on this combination (Marty et al. 2005). Unfortunately, the data in Marty et al was not sufficient to allow robust analysis of the cost effectiveness of this combination. We have amended the background information to clarify this situation.

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						In TA 34 an economic model developed by Roche based on one clinical study was accepted by the Appraisal committee, so it appears inconsistent for the GDG in this instance not to produce an economic model based on one RCT. As the GDG acknowledge in the Full guideline the trastuzumab/docetaxel combination is widely used and more clinically effective than trastuzumab/paclitaxel so it seems perverse not to recommend it. It should also be noted that the Appraisal committee recommended the combination of trastuzumab and paclitaxel despite a cost per QALY of £29,448. Given the similarity in price between docetaxel and paclitaxel and the statement in the guideline that the trastuzumab/docetaxel combination is more clinically effective than trastuzumab/paclitaxel one would expect a much more favourable cost/QALY.	
SH	Sanofi-Aventis	197.1	NICE	3		Systemic disease-modifying therapy – There is no reference to the use of combination chemotherapy in this section although it is referred to in section 1.3.3.2 on p 10. This may be misleading to a physician reading only this section of the document as there is an important sub-group of patients that may benefit from combination chemotherapy.	This page lists those recommendations from the guideline that the GDG agreed were the key priorities for implementation. The recommendation on combination chemotherapy was not voted as a key priority and hence is not present on this page.

SH	Sanofi-Aventis	197.11	Full	59	44-45	The guideline states that 'Trastuzumab in combination with paclitaxel (combination trastuzumab is currently only licensed for use with paclitaxel)….'. This statement is incorrect as docetaxel is also licensed for use in combination with trastuzumab – see trastuzumab and docetaxel SPCs for details. The recommendations should be amended to state that both taxanes can be used in combination with trastuzumab as has been acknowledged in the algorithm on page 30 of the NICE guideline.	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines. TA34 was published in 2002, at which time the statement regarding the licensed combinations for trastuzumab was correct, although we acknowledge that this is no longer the case. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	Sanofi-Aventis	197.12	Full	107	9	Table 11 1st column – it should read 0.5ml vial not 0ml vial	Thank you. This has been changed in the final version accordingly.
SH	Sanofi-Aventis	197.13	Full	111	40	Price discounts The NHS benefits from significant discounts vs. NHS list prices (usually >10%) on the majority of drugs it purchases. These discounts should be taken into account for all drugs purchased by the NHS rather than selectively. Consequently highlighting one discount system over another is inappropriate and a more general statement should be used such as "discounts available for drugs over NHS list prices should be taken into account as part of the decision making process." The costing tool to be produced in association with these guidelines should also include a similar statement. Also p53 L12-13 and P58 L7-8	We agree. However this was just one scenario explored in the one-way sensitivity analysis relating to paclitaxel. This was of particular concern to the GDG since paclitaxel was recently available in generic form. We were also advised that vinorelbine, above all others, is associated with a significant price discount.
SH	Sanofi-Aventis	197.14	Full	113	16	It should read 'in figure 4 below' not 'in figure 3 below'.	Thank you. The final version has been altered accordingly.

SH	Sanofi-Aventis	197.2	NICE (1.3.4.1)	59	44	The guideline states that 'Trastuzumab in combination with paclitaxel (combination trastuzumab is currently only licensed for use with paclitaxel)….' This statement is incorrect as trastuzumab and docetaxel are licensed for use in combination in advanced cancer (see point 12 for additional comments).	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines. TA34 was published in 2002, at which time the statement regarding the licensed combinations for trastuzumab was correct, although we acknowledge that this is no longer the case. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	Sanofi-Aventis	197.3	Full	3	16-24	There is no reference to the use of combination chemotherapy in this section although it is referred to in section 1.3.3.2 on p10 of the NICE guideline and the algorithm on p30 of the NICE guideline. Although this is not an option for all patients there is a sub-group for whom this may be the preferred choice. Physicians should be made aware that combination chemotherapy is another possible option for them to consider as stated elsewhere in the guideline.	This page lists those recommendations from the guideline that the GDG agreed were the key priorities for implementation. The recommendation on combination chemotherapy was not voted as a key priority and hence is not present on this page.
SH	Sanofi-Aventis	197.4	Full	51	17 and 25	It would be useful to directly reference the source trials for data or assumptions presented. Clarification of this with regards to line 17-28 would help the physician substantiate the statements. For example: Line 17 - reference is made to 2 small studies but it is unclear which these are from the list of 5 RCTs mentioned in line 12. Line 25 - reference is made to a large RCT which one might guess was Chlebowski et al from line 14 but with no certainty. To make the document fully transparent all results should be referenced as they would be in any peer	We will insert the references as suggested to aid clarity.

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						reviewed paper.	
SH	Sanofi-Aventis	197.5	Full	52	1-4	The guideline states: '*RCT evidence from three trials showed that first line treatment with combined therapies including an anthracycline and/or taxane, compared with the same anthracycline or taxane, provided no survival advantages but were associated with higher levels of adverse events. Quality of life outcomes were equivocal*.' This paragraph taken in full context is accurate, but the first sentence should take into account the referenced O'Shaughnessy et al 2002, Leonard et al 2002 and Miles et al 2004 papers of the docetaxel vs. docetaxel plus capecitabine study showing combination treatment provided a superior TTP and survival advantage. This issue can be resolved through appropriate referencing of supporting statements.	We believe that the paragraph as it stands is adequate.
SH	Sanofi-Aventis	197.6	Full	52	32-38	The guideline states: *'While it was acknowledged that there is no direct evidence comparing alternative chemotherapy sequences, the GDG considered it important to explore the cost effectiveness of plausible sequences using the best available data. An indirect treatment comparison methodology was an important component of this, but it was restricted to an assessment of the relative effectiveness of alternative first-line treatments based on the available RCT data.'* We agree that there is no direct evidence, of which we are aware, comparing alternative chemotherapy sequences and therefore agree with the GDG that the best approach is to develop a model using indirect comparisons to help address this issue.	Thank you
SH	Sanofi-Aventis	197.7	Full	54	32-37	The first sentence of this paragraph is confusing as it fails to distinguish between monotherapy and	The O'Shaughnessy et al., 2002 trial was the pivotal trial in TA62. The advanced breast cancer

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						combination therapy when referring to the studies conducted and the quality of the data. In the Evidence Review page 231 it states that: '*The evidence for capecitabine and docetaxel as a combination therapy remains centered on the RCT of O'Shaughnessy et al. (2002)*.'. It is therefore unclear why this study has not been mentioned and reference is only made to the study of Chan (2005). We suggest the first paragraph could be reworded as follows to address these 2 points: 'The level of evidence on the use of capecitabine (CAP) as a monotherapy is generally of poor quality consisting of low patient numbers, non-comparative phase II studies. As such, the findings from these studies should be viewed with caution. Evidence on the use of CAP in combination with docetaxel (DOC) is much stronger as it was based on three non-comparative phase II studies and two large comparative phase III RCTs involving 816 patients (O'Shaughnessy et al 2002 and Chan 2005).	guideline was tasked with updating TA62 and therefore only considered evidence published post 2002, hence the O'Shaughnessy 2002 trial is not included in the evidence base for this guideline.
SH	Sanofi-Aventis	197.8	Full	55	8-18	Line 8 - The guideline states: '*The RCT compared CAP + DOC with gemcitabine*..' which is incorrect. As stated in the Evidence Review (page 230) the comparison in the study by Chan (2005) was CAP+DOC vs GEM+DOC. Lines 15-18 - The last sentence in this paragraph is confusing. The retrospective analysis by Miles et al 2004 examined the effect of post study treatment on the survival of subjects who participated in the original study reported by O'Shaughnessy et al 2002. It should be made clear that the results described in lines 17-18 are based on the analysis of Miles et al 2004 not the original O'Shaughnessy study by appropriate referencing. (See p231 of the Evidence Review).	We have made this change. We have clarified the references

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SH	Sanofi-Aventis	197.9	Full	55	27-36	The current paragraph refers to the paclitaxel and doxorubicin data vs. FAC but does not include the study of Bontenbal (2005, JCO 23: 7081-7088) which includes data comparing docetaxel and doxorubicin vs. FAC. They conclude that treatment with docetaxel and doxorubicin results in a significantly longer TTP and OS and a higher objective overall response rate than FAC. Therefore we believe that this paragraph should be amended to include this data to provide fair balance.	Thank you. We have now included this paper in the evidence review. Guidelines are intended to cover the majority of clinical situations, not all possible situations. Anthracycline naïve patients who are fit for combination chemotherapy will constitute a relatively small subgroup of advanced breast cancer patients and therefore the guideline does not make recommendations on this. In unusual situations such as this we would expect clinical judgement to be used.
SH	Schering-Plough Ltd	198				This organisation was approached but did not respond.	
SH	Scotland Cancer Network (SCAN)	199				This organisation was approached but did not respond.	
SH	Scottish Intercollegiate Guidelines Network (SIGN)	200				This organisation was approached but did not respond.	
SH	Sheffield PCT	201				This organisation was approached but did not respond.	
SH	Sheffield Teaching Hospitals NHS Foundation Trust	202				This organisation was approached but did not respond.	
SH	Shropshire County and Telford & Wrekin PCT	203				This organisation was approached but did not respond.	
SH	Siemens Medical Solutions Diagnostics	204				This organisation was approached but did not respond.	
SH	Sigvaris Britain Ltd	205				This organisation was approached but did not respond.	
SH	Social Care Institute for Excellence (SCIE)	206				This organisation was approached but did not respond.	
SH	Society and College of Radiographers	207	Full	84	11-14	Does not include the option for stereotactic radiotherapy as an alternative to surgery and whole brain radiotherapy for a small subset of patients. There are a small number of patients for whom	No evidence comparing stereotactic radiosurgery with surgery was found, therefore the GDG were unable to make recommendations on this. This comment refers to an extremely small group of

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						surgery is very difficult but who have single metastases and others who prefer the option of external beam radiotherapy to invasive surgery. Stereotactic radiosurgery will be the subject of specialist commissioning through PCTs. If it is not in the NICE guidance as an alternative to surgery and whole brain it is very unlikely that patients will be able to access it.	patients. There is little or no data about the management of this precise situation and it is not covered in the guideline.
SH	Society for Academic Primary Care	208				This organisation was approached but did not respond.	
SH	South & Central Huddersfield PCTs	209				This organisation was approached but did not respond.	
SH	South East Wales Cancer Network	210.0	Full	35	1	If PET-CT has been used t diagnose metastases, then cannot see why it shouldn't be used to monitor response to therapy.	If a lesion has been confirmed by PET-CT as likely to be a metastasis, its subsequent response to treatment can be followed by standard CT imaging
SH	South East Wales Cancer Network	210.1	Full	52	22	Single agent weekly Paclitaxel should be mentioned here as an option to Docetaxel	We acknowledge there is clinical effectiveness data supporting the use of weekly paclitaxel. Unfortunately the necessary information from the Will Weekly Win trial was not available in time to be included in the health economic analysis.
SH	South East Wales Cancer Network	210.2	Full	59	44	Understand licence, must mention docetaxel in combination with trastuzumab here.	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines. TA34 was published in 2002, at which time the statement regarding the licensed combinations for trastuzumab was correct, although we acknowledge that this is no longer the case. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead.
SH	South East Wales Cancer	210.3	Full	60	3	Transtuzumab monotherapy should also be used in	This recommendation is from 'Guidance on the use

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	Network					patients either unfit for chemotherapy or who refuse chemotherapy.	of trastuzumab for the treatment of advanced breast cancer', NICE technology appraisal guidance 34 (2002).The recommendations from TA34 were formulated as part of that technology appraisal and not by the guideline developers. They have been incorporated into this guideline in line with NICE procedures for developing clinical guidelines, and the evidence to support the recommendations can be found at www.nice.org.uk/TA034. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead.
SH	South East Wales Cancer Network	210.4	Full	60	21	Very contentious. Suggest reconsider this in light of German Breast Group Trial	Trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data.
SH	South East Wales Cancer Network	210.5	Full	General		Many clinicians prefer oral form of Vinorelbine to IV. Oral vinorelbine has been recommended by the All Wales Medicines Strategy Group (AWMSG) for use within NHS Wales, and found to be cost-effective – see http://www.wales.nhs.uk/sites3/Documents/371/FAR%20Vinorelbine%20final.pdf	Investigating the cost effectiveness of oral versus IV vinorelbine was not identified as a priority by the GDG. The majority of the published evidence relates to IV administration.
SH	South West Kent Primary Care Trust	211				This organisation was approached but did not respond.	
SH	South West London SHA	212				This organisation was approached but did not respond.	
SH	Staffordshire Moorlands PCT	213				This organisation was approached but did not respond.	
SH	Stockport PCT	214				This organisation was approached but did not respond.	

SH	Sussex Cancer Network	215.0	Full	general		If you have any comments about these two definitions of HER2 positive status, for the two breast cancer populations, please comment This needs sorting out. Since all women have been tested at diagnosis for the last couple of years, the final 'early' definition should stand, as the other will become increasingly irrelevant, but clarity on whether retesting is ever required would be helpful	The GDG were unable to update TA34 as part of the advanced breast cancer guideline. Consequently the recommendations from TA34 were copied verbatim into the guideline, in accordance with NICE procedures for developing clinical guidelines.TA34 was published in 2002, and we acknowledge that the guidelines for HER2 testing have changed since that time. It has been decided that TA34 will be updated by NICE. Since this will happen during the lifetime of the advanced breast cancer guideline the recommendations from TA34 have been removed from the guideline and a cross reference inserted instead. This has resolved the issue that you have highlighted.
SH	Sussex Cancer Network	215.1	Full	general		We think this is a good document overall, but would like to see the section on links to specialist palliative care strengthened- only in passing in chapter 6, whereas lymphodema care gets a welcome focus	These issues have been covered by previous NICE guidance (Improving supportive and palliative care for adults with cancer, 2004) and are signposted within the recommendations. The GDG felt that it would be duplication to cover them again.
SH	Sussex Cancer Network	215.2	Full	58-61 And 22		**"Patients who are receiving treatment with trastuzumab should not continue trastuzumab at the time of disease progression outside of the central nervous system."** We have some concerns regarding this recommendation. Since the development of trastuzumab to treat metastatic breast cancer it has been apparent that there is synergy between trastuzumab and cytotoxic chemotherapy. In the pivotal registration study the response rate to single agent paclitaxel was 14%, to single agent trastuzumab was 17% but the response rate was 44% to the combination of these two agents (1). Since then a randomised second-line trial has been reported at the American Society of Clinical Oncology annual meeting 2008, and a final analysis presented at the European Society of Medical Oncology (2). One hundred and fifty-six women with HER2 over-expressing locally advanced or metastatic breast cancer were enrolled in this study. All women had previously received trastuzumab in the metastatic or	Trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data.

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						adjuvant settings and their disease had progressed. Women were randomised to receive single agent capecitabine chemotherapy (2500mg/m2 days 1-14, q21 days) or capecitabine plus trastuzumab (6mg/kg, q 21 days). After a median follow-up of 15.6 months those women receiving combination treatment had statistically significant improvements in response rates (48.1% vs 26.7, p=0.03), time to progression (8.2 vs 5.6 months, p=0.04) and clinical benefit rates (75% vs 54%). Overall survival also favoured the continuation of trastuzumab (25.5 vs 20.4 months) but has not reached statistical significance (p=0.26). No excess toxicity was seen in those women who received trastuzumab in addition to capecitabine. As a result of pre-clinical data, the studies described, and a substantial body of retrospective data, cytotoxic monotherapy in women with HER2 overexpressing metastatic breast cancer progressing on trastuzumab is not optimal therapy. This is perhaps best reflected in the fact that modern clinical trials in such women all include some form of HER2 targeted therapy given in addition to cytotoxic chemotherapy. 1. Slamon DJ et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer expresses HER2. New England Journal of Medicine 2001;344(11): 783-92. 2. Von Minckwitz G, et al. Capecitabine vs capecitabine +trastuzumab in patients with HER2 positive metastatic breast cancer progressing during trastuzumab treatment: The TBP phase III study (GBG 26/BIG 3-05). European Society of Medical Oncology 2008; Abs 133O.	
SH	Sussex Cancer Network	215.3	Full	61	12	There is a problem because the TA for trastuzumab is not being revised other than via this guideline,	Thank you. Your comments have been noted.

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						despite the fact that such guidelines do not have the mandatory force of TAs for PCTs, yet the TA for lapatinib is proceeding on the separate track but based on this recommendation for monotherapy at progression which is not common practice. Hence lapatinib must seem not to be cost effective, whereas it would be compared with TRZ plus capaecitabine. I raised the possibility of such issues at the scoping meeting some 3 years ago, but was overruled.	
SH	Tameside and Glossop Acute Trust	216				This organisation was approached but did not respond.	
SH	Tameside and Glossop PCT	217				This organisation was approached but did not respond.	
SH	Target Ovarian Cancer	218				This organisation was approached but did not respond.	
SH	Taunton Road Medical Centre	219				This organisation was approached but did not respond.	
SH	Thames Valley Cancer Network	220				This organisation was approached but did not respond.	
SH	Trafford Primary Care Trust	221				This organisation was approached but did not respond.	
SH	UK Anaemia	222				This organisation was approached but did not respond.	
SH	UK National Screening Committee	223				This organisation was approached but did not respond.	
SH	UK Specialised Services Public Health Network	224				This organisation was approached but did not respond.	
SH	University College London Hospitals (UCLH) Acute Trust	225.0	Full	General		Overall the guidance deals well with many difficult areas in the diagnosis and management of advanced breast cancer and will be valuable to al of those involved in the management of breast cancer. In places the document is highly prescriptive despite the lack of good evidence to justify the stance taken. It would be helpful if the guidance in such cases was offered in the form of advice rather than dictat. This is particularly true of the "NICE version". At the end of	Thank you We agree that there is no single "right" way to treat advanced breast cancer. Stakeholders had input into which topics the guideline investigated. Where the evidence was limited, GDG consensus was used to create recommendation in accordance with

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						the day there is no "right" or "wrong" way to treat advanced breast cancer and it is particularly important to respect patient attitudes and preferences when it comes to treatment. No mention is made of the importance of specialist nursing support for this group of patients is made in contrast to those with early disease. As the guidance does not claim to be comprehensive there should be a mechanism for its incorporation into local generated guidelines and for its updating as Breast Cancer is a rapidly evolving field	NICE methodology. This document is a guideline and not a mandatory approach to clinical practice. As such it does not replace clinical judgement. We have re-iterated the NICE Improving Outcomes Guidance on breast cancer (2002) with regard to mechanisms to promote continuity of care, in particular provision of a key worker. In many cases this role might be best filled by a specialist nurse. We agree but this will be a matter for local implementation. The guideline will be reviewed at intervals, in accordance with NICE methodology, to determine if an update is required to take into account new evidence.
SH	University College London Hospitals (UCLH) Acute Trust	225.1	Full	33 1.1.1.8	23	It is very well established that reliability of HER2 testing on archival specimens by IHC may be adversely affected by fixation issues and as receptor status can change, a fresh biopsy is sometimes preferable.	This is a matter for local protocols, we do not feel it needs to be stated in the guideline
SH	University College London Hospitals (UCLH) Acute Trust	225.2	Full	47 1.3.2.2	6	There is good trials evidence that the combination of tamoxifen & goserelin gives superior progression free survival to tamoxifen alone and this combination should therefore be allowed as an initial treatment option for pre-menopausal women.	There is one randomised trial comparing buserelin in combination with Tamoxifen with either agent alone. This is a relatively small study, and no confirmatory trial has been performed. However on review of this evidence the GDG felt that the recommendation should be changed as suggested.
SH	University College London Hospitals (UCLH) Acute Trust	225.3	Full	52 1.3.3.3	18	The sequence of chemotherapy recommended is concordant with much of routine clinical practise but there are frequently reasons for deviation from this schema. For instance docetaxel is dangerous for women with impaired liver function whilst paclitaxel, especially given weekly is much safer. Older women may have difficulty with taxane side effects and may prefer non-epilating treatments. It would therefore be better if this is a suggested rather than mandated sequence.	This document is a guideline and not a mandatory approach to clinical practice. As such it does not replace clinical judgement.
SH	University College London	225.4	Full	53	32	It seems illogical that paclitaxel-gemcitabine, which is	The combination of gemcitabine/paclitaxel was not

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	Hospitals (UCLH) Acute Trust		Appendix 1	58 1.3.3.3	2	recommended by NICE in TA116 was excluded from this analysis on the grounds that the GDG thought it should not be used whilst docetaxel-gemcitabine, which has not been considered by NICE was considered in the economic analysis in appendix 1 used to derive the recommendation on chemotherapy sequence.	included in the economic analysis because its cost-effectiveness had already been analysed as part of TA116.
SH	University College London Hospitals (UCLH) Acute Trust	225.5	Full	60 1.3.4.4	21	The GBG26 study with trastuzumab-capecitabine and the EGF100151 study with lapatinib-capecitabine both provide clear evidence that continuation of HER2-targeted therapy beyond systemic progression on trastuzumab is beneficial. There are in addition a number of non-randomised studies of chemotherapy-trastuzumab combinations and "practise or community audits", not of all of which are cited here, that support continuation. The relative merits of lapatinib (which is the subject of a separate STA) and trastuzumab in this setting are not established. It does not however seem justified to reject continuation trastuzumab on grounds of inadequate evidence and whilst it may well fail NICE economic tests, these have not been considered here.	Trastuzumab is not currently licensed for this indication. It would be difficult to make a positive recommendation for this high cost intervention without good cost-effectiveness data.
SH	University College London Hospitals (UCLH) Acute Trust	225.6	Full	61 4.3	10	See comment 6. This would be an enormously expensive study that is unlikely to generate much more that a lower "p" value than the GBG26 study, but would reduce research funding available for other important studies in breast and other cancer types.	The reported studies are small. The GBG-26 study has yet to demonstrate a statistically significant improvement in overall survival. Cost-effectiveness data from these studies has yet to be made available. At this point it is not possible to know if the data that will be made available from these studies will be adequate to perform good quality cost-effectiveness analysis. Trastuzumab is an extremely high cost treatment and it would be inappropriate for patterns of use to change until adequate research demonstrating its cost effectiveness has been performed. We have amended these research recommendations to include collection of data required for prospective cost effectiveness

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							analysis.
SH	University College London Hospitals (UCLH) Acute Trust	225.7	Full	84 1.5.5.1	11	1. The option of radiosurgery in patients who would be considered for surgery (< 3 mets, controlled systemic disease, good PS) but who have surgically inaccessible lesions should be included. This population is likely to increase with better systemic treatment options. 2. The role of whole brain RT following radiosurgery or surgery is still debated; it clearly contributes to local control but little if anything to overall survival. The risk/benefit of WBRT with respect to cognitive decline vs local tumour recurrence in relatively good prognosis patients is still unknown.EORTC 22952 addresses this (across all histologies) and will report in 2009. I would not want to see a blanket recommendation for WBRT without seeing these data.	This comment refers to an extremely small group of patients. There is little or no data about the management of this precise situation and it is not covered in the guideline. For stereotactic radiosurgery in general, the GDG felt that the quality of the data was not sufficient to make a more general recommendation about its use at this time, but a recommendation for further research has been made. On the basis of the currently available data, the GDG feels that its current recommendation is appropriate. Clearly this may need to be reviewed in future if new evidence is published.
SH	University Hospitals Coventry & Warwickshire NHS Trust	227				This organisation was approached but did not respond.	
SH	University of Birmingham, Department of Primary Care & General Practice	228				This organisation was approached but did not respond.	
SH	Velindre Acute Trust	229				This organisation was approached but did not respond.	
SH	Walsall PCT	230				This organisation was approached but did not respond.	
SH	Welsh Assembly Government	231				This organisation responded and said they have no comments to make	Thank you
SH	Welsh Scientific Advisory Committee (WSAC)	232				This organisation was approached but did not respond.	
SH	Wessex Cancer Trust	233				This organisation was approached but did not respond.	

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SH	West London Cancer Network	234				This organisation was approached but did not respond.	
SH	Western Cheshire Primary Care Trust	235				This organisation was approached but did not respond.	