NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Lapatinib for women with previously treated advanced and metastatic breast cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patient/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee. Where clinical specialists and patient experts make comments on the ACD separately from the organisations that nominated them, these are presented alongside the consultee comments in the tables below.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

Comments received from consultees

Consultee	Comment	Response
GlaxoSmith-Kline (GSK)	**1. <u>Do you consider that all of the relevant evidence has been taken into account?</u>** There are two significant aspects of the evidence base that we do not believe have been fully considered. Firstly, we believe that the ACD fails to take sufficiently into account reports provided by clinical and patient groups, nominated experts, and clinical experts advising the Evidence Review Group (ERG) as part of the STA process, which support GSK's evidence that trastuzumab is continued beyond progression in this setting. Further details are provided in Section 1.1 below.	The Committee has considered the evidence about the proportion of people continuing trastuzumab following progression of disease. See FAD sections 3.14, 4.2 and 4.3.
GSK	Secondly, since our original submission in April 2007 there have been considerable and fundamental changes to the evidence base that address areas of uncertainty highlighted by the Appraisal Committee. GlaxoSmithKline submitted a dossier to NICE for lapatinib on 17 April 2007. At this time it was anticipated that marketing authorisation would be forthcoming from the EMEA during Quarter 3 2007. Due to several regulatory delays, CHMP positive opinion was first granted on 13 December 2007 and again on 24 April 2008, with marketing authorisation following on 10 June 2008. Therefore there has been a significant interval between GSK's submission in April 2007 and its review by the Evidence Review Group during May 2007, the Appraisal Committee meeting at which the evidence was considered on 22 January 2008, and the current consultation period in July 2008.	The additional evidence provided by GSK has been reviewed by the DSU. It has also been considered by the Committee and is included in the FAD. See FAD sections 3.4, 3.5, 3.14 to 3.24 and 4.8, 4.11, 4.14, 4.15.
GSK	Whilst we acknowledge that the STA process is intended to provide guidance to the NHS on technologies as soon as possible after they become available on the market, the resulting need to perform the evidence review in parallel with licensing can cause significant issues when the process is delayed and the evidence base for the technology and its comparators develops significantly over time, as is the case for lapatinib. We strongly believe that these changes in the evidence base should be considered by the Appraisal Committee before issuing final guidance, and therefore we are submitting them for consideration as part of our response to the ACD.	The additional evidence provided by GSK has been reviewed by the DSU. It has also been considered by the Committee and is presented in the FAD. See FAD sections 3.4, 3.5, 3.14 to 3.24 and 4.8, 4.11, 4.14, 4.15.

Consultee	Comment	Response
GSK	The ACD states that there was a lack of evidence to support the justification of trastuzumab containing regimens beyond progression as comparators in this setting (Section 4.9, Consideration of the Evidence). GSK provided in its original submission results from two key market research studies performed in the UK to determine current service provision for patients with advanced or metastatic breast cancer (IMS Oncology Analyzer study, independently collected patient record data from January 2004 to September 2006; Dendrite Docscan Oncology Survey, physician-based survey of prescribing behaviour undertaken in August 2006). These studies suggested that trastuzumab was used widely beyond disease progression in UK clinical practice at that time (in 40-45% of patients).	The Committee has specifically considered the use of trastuzumab after progression of disease. It was persuaded by the evidence submitted and the testimony from the clinical specialists that it should consider the clinical- and cost-effectiveness analyses that included trastuzumab as a comparator. See FAD sections 3.14, 4.2 and 4.3.
GSK	We acknowledge the limitations of the analyses highlighted by the ERG and in the ACD, in particular the small sample size that was included in the IMS Oncology Analyzer study (24 patients who fitted the criteria for inclusion). However, the data are in the form of patient-level notes reviews, provided anonymously by physicians. The 24 eligible patients were identified from 1,410 patients with metastatic breast cancer in the database. We believe that despite the limited numbers these anonymously submitted patient-level results are possibly more reflective of real practice than anecdotal evidence which will be influenced by concerns about highlighting the unlicensed use of trastuzumab beyond progression. These data are supported by the ERG's clinical advisors who confirmed that trastuzumab is continued beyond progression in conjunction with either capecitabine or vinorelbine, whereas trastuzumab monotherapy is rarely used beyond disease progression (Section 2.3.3, ERG report), and concluded that the selected comparators in GSK's evaluation were appropriate (Section 3.1.2, ERG report).	The Committee has specifically considered the use of trastuzumab after progression of disease. It was persuaded by the evidence submitted and the testimony from the clinical specialists that it should consider the clinical- and cost-effectiveness analyses that included trastuzumab as a comparator. See FAD sections 3.14, 4.2 and 4.3.

Consultee	Comment	Response
GSK	This is also consistent with statements by patient and physician groups, as well as nominated experts which formed part of the Evaluation Report underpinning the Appraisal Committee's deliberations. These written comments are particularly relevant as from the ACD documentation it would appear that a medical oncologist did not attend the Appraisal Committee discussions. Whilst trastuzumab is only licensed for use up to disease progression in the metastatic setting, it is our understanding that this practice has come about due to the acceptance of the importance of continuing to suppress the ErbB2 receptor and the lack of alternative ErbB2-targeted treatments. The ACD refers to the view of clinical experts that the practice varies considerably across England and Wales. Whilst we acknowledge that variability does exist, the written expert submissions do support that it is used and with almost 50% of patients receiving this option it should not be discounted as a valid comparator from the appraisal. Further, we note that the ACD highlights the requirement for research to compare lapatinib with trastuzumab in this setting, which would not be appropriate if this was not a relevant comparator. We acknowledge that capecitabine regimens are also a valid comparator although updated data (reported below) would question whether these remain the most commonly used. GSK therefore defends the original assumption that at that time of our original submission, trastuzumab-containing regimens were routinely continued beyond progression, in nearly half of patients in this setting.	The Committee has specifically considered the use of trastuzumab after progression of disease. It was persuaded by the evidence submitted and the testimony from the clinical specialists that it should consider the clinical- and cost-effectiveness analyses that included trastuzumab as a comparator. See FAD sections 3.14, 4.2 and 4.3.

Consultee	Comment	Response
GSK	1.1.1. *New market research data supporting the use of trastuzumab beyond progression* Since the original market research studies were performed in 2004-2006 there are more data available in the IMS Oncology Analyzer database on which to base conclusions regarding clinical practice. The original analysis has been expanded to a 2 year period covering 2006-2007, which is more up-to-date and therefore more reflective of current practice, and includes a greater number of relevant patient records (n=98) from a larger pool of metastatic breast cancer patients (n=2,815). In response to the original IMS data the ACD noted that it was not clear which hospitals the data relate to, and whether different regions or specialist hospitals could be over- or under-represented. Full details of the regional distribution, as well as the respondents' description of their place of work (university hospital, non-university hospital, or both) are given in Appendix 1 for these new market research data. We believe that the data are not over-representative of any particular UK region, or any particular type of hospital. The results suggest that trastuzumab is now used beyond progression in around 55% of patients, the main regimens being in combination with either capecitabine or vinorelbine (Table 1.1). These patient-level results are supported with striking consistency by a market research survey undertaken with Cegedim Dendrite (fielded April-June 2008), at oncology consultant-level, to provide insight into current practice (Table 1.1; see Appendix 1 for further details). **Table 1.1 Updated IMS Oncology Analyzer and Cegedim Dendrite Market research results*** ***(provided but not reproduced here)***	The updated market research data has been considered by the Committee and is included in the FAD. See FAD sections 3.14, 4.2 and 4.3.

Consultee	Comment	Response
GSK	The recent revised NICE methods guide states that unlicensed comparator technologies may be considered if they are used routinely in the NHS. Available evidence updated in this response demonstrates that currently regimens containing trastuzumab are the most likely therapeutic option for patients in the UK, in the absence of an alternative ErbB2-targeted therapy; the use of this option is clearly recognised by patient groups and clinicians in their advice and submissions to this appraisal. Furthermore, the recent publication of the first phase III randomised controlled clinical trial data supporting the effectiveness of trastuzumab used in this setting (GBG 26/BIG 3-05) is likely to support the continued use of this therapeutic approach (see below). Indeed, our clinical advisers suggest that such practice will continue to increase over time on the basis of this trial. In conclusion, we believe that the more recent evidence improves the robustness of our assumption that trastuzumab containing regimens are relevant comparators in this setting, and are now used in around 55% of patients. We believe that this evidence should be considered by the Appraisal Committee.	The Committee has specifically considered the use of trastuzumab after progression of disease. It was persuaded by the evidence submitted and the testimony from the clinical specialists that it should consider the clinical- and cost-effectiveness analyses that included trastuzumab as a comparator. See FAD sections 3.14, 4.2 and 4.3.

Consultee	Comment	Response
GSK	**1.2. Evidence on the clinical effectiveness of trastuzumab beyond progression** The ACD highlighted the lack of randomised trial evidence on the use of trastuzumab beyond progression as a significant concern in their consideration of the evidence, concluding that the clinical effectiveness of trastuzumab in patients who have disease progression on treatment was unproven, and that the unadjusted indirect comparison method used resulted in uncertainty surrounding the cost-effectiveness estimates. Whilst we would argue that there was some evidence of trastuzumab efficacy in this setting at the time of our original submission, we recognise that the quality of evidence was limited by the nature of the uncontrolled studies that provided the only data at the time. Further, as acknowledged by the ERG, the use of these data in an unadjusted indirect comparison was unavoidable due to the lack of randomised data. However, on 3 June 08 the statistical results of the only randomised controlled trial (GBG 26 / BIG 3-05)[1,2] investigating continuation of trastuzumab beyond progression in a setting similar to the current indication for lapatinib (i.e. following progression on trastuzumab administered for metastatic disease),were presented at the American Society of Clinical Oncology Annual Meeting (ASCO). These results now allow a more robust comparison with lapatinib than was possible at the time we submitted in April 2007. This study was identified by the ERG (see p25 of their report) as an ongoing study, and was also identified in GSK's systematic review which was updated to March 2008 (Appendix 2, section 2.1).	The evidence from the GBG26 trial has been considered by the Committee and is presented in the FAD. See FAD sections 3.5, 4.4 and 4.11.

Consultee	Comment	Response
GSK	Given that the evidence base for the efficacy and extent of use of trastuzumab beyond progression was stated to be a key consideration for the Appraisal Committee in making their decision, we offered NICE the opportunity to consider the above additional evidence (together with an extended pooled analysis of uncontrolled trastuzumab studies identified by an updated literature search, as well as the most recent lapatinib overall survival data cited in the Summary of Product Characteristics, for completeness) prior to releasing the ACD to aid a more productive consultation. This offer was rejected in order to maintain the planned timelines for the appraisal. We believe that, in order to make a decision on the appropriate use of lapatinib in the context of regulatory delays and a rapidly evolving evidence base, the most up-to-date evidence should be considered by the Appraisal Committee. These new data and their implications are summarised below.	The evidence from the GBG26 trial and the extended pooled analysis have been considered by the Committee and are presented in the FAD. See FAD sections 3.5, 4.4 and 4.11.
GSK	*1.2.1. New randomised data comparing trastuzumab plus capecitabine with capecitabine alone - study GBG 26 / BIG 3-05* Summary results from the GBG 26 study are presented in Table 1.2 alongside those from the latest results for the lapatinib pivotal study (EGF100151). Further details of the GBG 26 study design can be found in Tables 1-5, Appendix 2. **Table 1.2: Summary of key findings from EGF100151 and GBG 26 (Von Minckwitz 2008)** ***(provided but not reproduced here)***	The evidence from the GBG26 trial and the updated evidence from the EGF100151 trial have been considered by the Committee and are presented in the FAD. See FAD sections 3.4, 3.5 4.4 and 4.11.

Consultee	Comment	Response
GSK	The primary endpoint of the GBG 26 study was time to progression; it was planned to recruit 241 patients per arm to show an improvement from 4 to 5.1 months by continuing trastuzumab. The study closed early on the advice of the study's Independent Data Monitoring Committee due to slow accrual, having recruited only a third of its planned patients (N =156 of 482-patient target); statistical analyses were carried out. Notably, the FDA registration of lapatinib was cited by the authors as a reason for the study not to reach target recruitment. The results show that trastuzumab in combination with capecitabine is clinically effective when compared with capecitabine alone, with significantly improved median time to progression (TTP), overall response rate (ORR) and clinical benefit rate (CBR). Overall survival was not significantly different in the two treatment groups. Although the absolute values for the trastuzumab plus capecitabine combination appear to be numerically higher than those for lapatinib plus capecitabine, it should be noted that patients in the GBG 26 study were less advanced in the course of their disease having received a maximum of only one prior line of chemotherapy for metastatic disease[1], whereas more than 50% of patients in the EGF100151 study had previously received at least four prior lines of therapy in the metastatic setting. This also appears to be reflected in the higher efficacy results for the capecitabine monotherapy arm in the GBG 26 study compared with those for the capecitabine monotherapy arm at the same dosage in EGF100151. These results support the efficacy of trastuzumab in this setting, as suggested in GSK's original pooled analysis (weighted mean TTP 5.0 months (95%CI: 4,3, 5.8 months); HR 0.86 (95%CI: 0.74, 1.01)). The GBG 26 study[1,2] is the first randomised controlled trial to have evaluated the continued use of trastuzumab beyond progression in a setting similar to the licensed setting for lapatinib. Whilst there are some limitations to the study, specifically relating to its early closure and the small number of patients recruited, it clearly confirms the value of continuing to suppress ErbB2 in receptor-positive patients and that, in the absence of an alternative ErbB2-targeted therapy, continuation of trastuzumab beyond progression is a reasonable clinical approach. In addition, it allows the use of more robust data to generate cost effectiveness estimates for the use of lapatinib plus capecitabine compared with trastuzumab beyond progression, and hence reduce the uncertainty around the estimates for consideration by the Appraisal Committee.	The evidence from the GBG26 trial and the updated evidence from the EGF100151 trial have been considered by the Committee and are presented in the FAD. See FAD sections 3.4, 3.5, 4.4 and 4.11.

Consultee	Comment	Response
GSK	*1.2.2. Additional, uncontrolled trastuzumab studies* The systematic review of clinical literature was updated from a cut-off of February 07 to March 2008. The review identified one new randomised controlled trial as meeting the eligibility criteria: the German Breast Group study (GBG 26) comparing trastuzumab plus capecitabine versus capecitabine monotherapy.[1,2] This study is described above. An additional ten non-randomised studies[4-14] involving the use of trastuzumab beyond progression were identified as meeting the inclusion criteria in the updated systematic review conducted in March 2008. These studies were either single-arm phase II trials or observational studies, the majority of which were conducted retrospectively. Several of the studies involved small patient numbers and/or were conducted at single centres and in single countries. In addition, many are reported only as abstracts and therefore provide limited information on the participant characteristics. Further details on the individual study designs and baseline characteristics can be found in Tables 1 and 2 in Appendix 2. The growing number of studies identified which involve the continuation of trastuzumab beyond disease progression supports the case that this has been a commonly employed therapeutic approach in the absence of alternative ErbB2-targeted agents. The main efficacy and safety findings for the new non-randomised studies identified via the systematic review are summarised in Tables 3 to 5 in Appendix 2. Although the absence of a control group and lack of statistical dispersion data around the outcomes reported limit the validity of these study findings, their results support the rationale for continuing ErbB2-targeted therapy after progression on trastuzumab.	Comments noted. The updated pooled estimate for the effectiveness of trastuzumab when used following progression of disease has been considered by the Committee and is presented in the FAD. See FAD sections 3.5, 4.4 and 4.11.

Consultee	Comment	Response
GSK	Five of the newly identified studies2,4-7 report a time to second progression and these data have been included in an updated pooled analysis (with weighting applied to account for sample size) conducted in a similar manner to that undertaken for our original submission, to estimate a pooled median TTP for trastuzumab-based therapy beyond progression. The final number of studies included in this updated analysis was sixteen, since one of the original studies7 was an update of data previously included in the original analysis, so the original study was omitted. Although it was not possible to differentiate between the efficacy of different trastuzumab-containing regimens, this yielded a pooled estimate of median TTP of 27.0 weeks (95% CI: 23.3, 31.1) [6.2 months (95%CI: 5.4, 7.2)], and a hazard ratio of 0.70 (95% CI: 0.61, 0.81). The addition of these studies increases the magnitude of efficacy in comparison with the original pooled analysis (see section 1.2.1 for original results). The disaggregated and pooled results from these studies can be found in section A2.2 in Appendix 2.	Comments noted. The updated pooled estimate for the effectiveness of trastuzumab when used after disease progression has been considered by the Committee and is presented in the FAD. See FAD sections 3.5, 4.4 and 4.11.
GSK	**1.3. Evidence on the clinical effectiveness of lapatinib** The Summary of Product Characteristics (SmPC, section 5.1) now presents a later survival analysis than that presented in our original submission. This updated analysis for overall survival was conducted on 28 September 2007 (see Table 1.3 below for a comparison of the two analyses). These data were provided to NICE in the form of an addendum to the submission on 2 May 2008, which contained further detail of the analysis. **Table 1.3: Summary of overall survival (ITT population, April 2006 and September 2007 cut-offs)** ***(included but not reproduced here)***	The updated evidence from the EGF100151 trial has been considered by the Committee and is presented in the FAD. See FAD sections 3.4 and 4.11.
GSK	Despite an increase in the median overall survival benefit for lapatinib plus capecitabine versus capecitabine (8.1 weeks difference for the September 2007 cut-off; 1.1 weeks for the April 2006 cut-off), the hazard ratio has increased slightly, and the difference remains non-significant. The impact of these updated results on the cost effectiveness of lapatinib in combination with capecitabine is explored below in section 1.4.	The updated evidence from the EGF100151 trial has been considered by the Committee and is presented in the FAD. See FAD sections 3.4 and 4.11.

Consultee	Comment	Response
GSK	**1.4. Impact of developments in the evidence base on the cost effectiveness of lapatinib in combination with capecitabine** Having presented new and updated data we believe that it is important to show how these developments in the evidence base impact on the cost effectiveness results presented in GSK's original submission. Table 1.4 summarises the impact on costs and effects of lapatinib and comparators associated with the evolving evidence base, as well as the change from an assumed price of £11.00 per tablet (in the original submission) to the final list price of £11.49 per tablet. Due to some minor corrections to the economic model to address errors that were discovered after GSK made our original submission the original base case results have changed marginally (shown in Scenario 2; details of minor corrections to the model are included in Appendix 3). All analyses from Scenario 3 onwards have been performed using the corrected model. The assumptions for each scenario are described as follows: *Scenario 1 (original base case; original model):* - Lapatinib list price £11.00 per tablet - Overall survival data April 2006 cut-off - Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies) *Scenario 2 (original base case; corrected model):* - Lapatinib list price £11.00 per tablet - Overall survival data April 2006 cut-off - Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies) *Scenario 3* - Lapatinib list price £11.49 per tablet (current list price) - Overall survival data April 2006 cut-off Efficacy for trastuzumab comparator regimens from original pooled analysis (11 studies)	The updated economic analysis has been considered by the Committee and the results are summarised in the FAD. The Committee's interpretation of the cost effectiveness of lapatinib has been made based on the revised analyses submitted by GSK. See FAD sections 3.14 to 3.17 and 4.8 to 4.15.

Consultee	Comment	Response
GSK	*Scenario 4* - Lapatinib list price £11.49 per tablet (current list price) - Overall survival data April 2006 cut-off - Efficacy for trastuzumab comparator regimens from updated pooled analysis (16 studies) *Scenario 5* - Lapatinib list price £11.49 per tablet - Overall survival data September 2007 cut-off (most recent data cited in SmPC) - Efficacy for trastuzumab comparator regimens from updated pooled analysis (16 studies) *Scenario 6 (fully updated price and clinical results)* - Lapatinib list price £11.49 per tablet - Overall survival data September 2007 cut-off - Efficacy for trastuzumab comparator regimens from Von Minckwitz study* The methodology for estimating the hazard ratios for this study, for incorporation into the economic modelling, are detailed in Appendix 4. **Table 1.4. Summary of impact of assumptions revised from original base case due to developing evidence base** ***(included but not reproduced here)***	The revised economic analysis has been considered by the Committee and the results are summarised in the FAD. The Committee's interpretation of the cost effectiveness of lapatinib has been made based on the revised analyses submitted by GSK. See FAD sections 3.14 to 3.17 and 4.8 to 4.15.

Consultee	Comment	Response
GSK	It is clear from these scenario analyses that incorporating the most recent and robust data sources into the cost effectiveness evaluation confirms the results of our original base case: lapatinib in combination with capecitabine remains highly cost effective compared with trastuzumab-containing regimens in this setting; lapatinib is not cost effective when compared with single agent chemotherapies (capecitabine or vinorelbine). We believe that Scenario 6 provides the most robust estimate as it is based on randomised trial data. However, if Scenario 5 was preferred (using efficacy for trastuzumab comparator regimens from the updated pooled analysis) the estimates would further favour lapatinib and hence the use of Scenario 6 also provides the more conservative approach. Probabilistic sensitivity analysis (PSA) was performed on Scenario 6 with the same probability distributions, means and standard errors as used in our original submission. In summary these analyses suggest that the likelihood of lapatinib plus capecitabine having an incremental cost-utility ratio lower than £20,000/QALY when compared with capecitabine or vinorelbine monotherapies is negligible (under 1%); (2-6% for a threshold of £30,000/QALY). The likelihood that lapatinib plus capecitabine has an incremental cost-utility ratio lower than £20,000/QALY when compared with trastuzumab-containing regimens is over 90% (from 85-93% for the £30,000 threshold).	The revised economic analysis has been considered by the Committee and the results are summarised in the FAD. The Committee's interpretation of the cost effectiveness of lapatinib has been made based on the revised analyses submitted by GSK. The Committee considered that these data demonstrated that the comparison of lapatinib with trastuzumab containing regimens was based on a comparison of capecitabine with trastuzumab containing regimens which was not cost effective. The Committee concluded that the result of the cost-effectiveness analysis for laptatinib versus trastuzumab was based on a comparison of trastuzumab versus capecitabine which was not cost effective and was therefore not supportable. See FAD section 4.13.
GSK	GSK believes that the interpretation of the pivotal clinical trial EGF100151 is reasonable. We agree with the ACD's conclusion that whilst lapatinib in combination with capecitabine is clinically effective when compared with capecitabine monotherapy, it is not cost effective in this comparison, nor when compared with vinorelbine monotherapy.	Comments noted, no actions required.

Consultee	Comment	Response
GSK	However, we have significant concerns about the interpretation of the cost effectiveness evidence versus trastuzumab-containing regimens submitted by GSK. The ACD refers to scenario analyses performed by the ERG to evaluate the impact of changing assumptions that relate to the lifetime costs of comparator regimens. Responses to these analyses are discussed individually below, and summarised thereafter.	The additional economic analysis provided by GSK has been considered by the Committee and the results are summarised in the FAD. The Committee's interpretation of the cost effectiveness of lapatinib has been based on the revised analyses submitted by GSK. See FAD sections 3.15 to 3.17 and 4.8 to 4.15.
GSK	The ERG notes that it is not clear why the weight and BSA distributions from the main trial were not used directly, rather than inferring distributions based on the trial mean and standard deviation; they conducted an exploratory analysis on this issue, which we believe under-estimates the true level of wastage of trastuzumab. The method used in GSK's model was intended to facilitate the use of alternative estimates of mean weight and BSA as user inputs, and also to facilitate switching between 'with wastage' and 'no wastage' scenarios. The assumption of lognormal distribution of weight and BSA was based on inspection of the two distributions, showing them to be truncated at zero and skewed to the right. The parameterized lognormal distributions fit the actual distributions remarkably well (see GSK's response to the ERG report for details). We believe that the use of the parameterized lognormal distributions rather than the actual weight distributions was a reasonable approach. A comparison of the estimated mean dose for trastuzumab and vinorelbine assuming no wastage, assuming wastage based on the lognormal distribution, and assuming wastage based on the mean (ERG approach) in Table 2.1 suggests that the approach employed by the ERG generates an estimate of vinorelbine use that is similar to that generated by the original model. For trastuzumab the approach employed by the ERG generates estimates of use per dose that are greater than those obtained assuming no wastage, but less than those generated using the lognormal distribution. **Table 2.1. Comparison of estimated doses assuming no wastage, and wastage based on the lognormal distribution and ERG methodology** ***(Included but not reproduced here)***	Comments noted. The Committee's interpretation of the cost effectiveness of lapatinib has been based on the revised analyses submitted by GSK. See FAD sections 3.15 to 3.17 and 4.8 to 4.15.

Consultee	Comment	Response
GSK	We acknowledge that attempts are made to batch-produce trastuzumab infusions and minimise drug wastage, but since the trastuzumab SmPC specifies that vials are for single use it would seem highly unlikely that wastage can be avoided altogether. Therefore to understand the extent of trastuzumab wastage we commissioned independent market research with 24 oncology pharmacists from 17 UK cancer networks (July 2008; Taylor Nelson Sofres) to understand the policies adopted regarding single use vials, and to quantify the proportion of trastuzumab for metastatic breast cancer that is wasted (further details are presented in section 1.1.3 of Appendix 1). Results indicated that 46% of respondents have a policy relating to the repeat use of IV vials and consider all to be single use. Thirty three percent have a policy and consider some IV vials for multiple use (where possible). The remainder have no policy relating to repeat use of IV vials. Participants were asked to estimate the proportion of total trastuzumab that is discarded, i.e. wasted, in the treatment of metastatic breast cancer patients. On average respondents estimated that 15% of trastuzumab used for the treatment of metastatic breast cancer is wasted (range 5%-60%). We believe that to exclude wastage would be extreme, and that the estimate of 15% trastuzumab wastage is most likely to reflect true clinical practice. We have therefore incorporated this level of wastage into scenario analyses presented below, by applying an inflation factor to the acquisition costs of trastuzumab (Section 2.5).	The Committee considered the revised assumptions about trastuzumab wastage and administration proposed by GSK in the economic model. The Committee also heard evidence from clinical specialists. Clinical specialists considered that an assumption that 15% of trastuzumab was wasted may still be an overestimate. The Committee also heard that administration of trastuzumab once every 3 weeks was standard clinical practice. The Committee therefore concluded that although the revised assumptions about trastuzumab wastage and administration reduced the overall costs of trastuzumab treatment, these costs may still be overestimated. See FAD sections 3.15, 4.12.

Consultee	Comment	Response
GSK	We strongly disagree with the use of the lower trastuzumab administration cost of £117 as suggested by the ERG. Trastuzumab administration costs in GSK's original submission (£245.22) were taken from NHS Reference Costs 2006,[15] the most current available at the time. The cost includes the cost of an outpatient chemotherapy consultation £207.22 (interquartile range £171 to £277). In addition the handling cost of a complex IV infusion (£38) was added.[16] The cost suggested by the ERG (£117) is referenced to a medical oncology outpatient consultation of £109 (Netten and Dennett 1999)[17] uplifted to 2006 prices. We believe that the most recent costs published by the Department of Health at the time of the submission are far more robust than those calculated almost a decade ago, and we vigorously defend our original assumption of £245.22.	Comment noted. The original cost of £245.22 used in the original manufacturer's model was used for the purpose of decision making.

Consultee	Comment	Response
GSK	The ERG scenario analysis assumed that all patients receive trastuzumab on a three-weekly schedule (6mg/kg). Our original assumption was that trastuzumab is administered once-weekly (2mg/kg), in accordance with NICE guidance and the SmPC for trastuzumab treatment of metastatic breast cancer. However, in recognition of the use of the three-weekly administration schedule by some practitioners, despite this schedule being licensed only for early breast cancer, we supplied a deterministic sensitivity analysis in our original submission. To further address this issue, as highlighted by the ERG, we tested the assumption in the market research with oncology pharmacists described above (and in section 1.1.3 of Appendix 1). Respondents fed back that an average of 11.6% of trastuzumab in metastatic breast cancer is given weekly (range 0% to 100%; standard deviation of mean = 29.3%). Therefore we have applied the figure of 11.6% weekly/88.4% 3-weekly trastuzumab to the scenario analyses below (Section 2.5).	The Committee considered the revised assumptions about trastuzumab wastage and administration proposed by GSK in the economic model. The Committee also heard evidence from clinical specialists. Clinical specialists considered that an assumption that 15% of trastuzumab was wasted may still be an overestimate. The Committee also heard that administration of trastuzumab once every 3 weeks was standard clinical practice. The Committee therefore concluded that although the revised assumptions about trastuzumab wastage and administration reduced the overall costs of trastuzumab treatment, these costs may still be overestimated. See FAD sections 3.15, 4.12.

Consultee	Comment	Response
GSK	In the absence of randomised comparative evidence on the efficacy of trastuzumab, the ERG performed an analysis whereby the hazard ratio for progression free survival with trastuzumab was based on a lower median TTP than that obtained from the original pooled analysis. It is not clear from the ERG's report what the actual hazard ratio fed into the model was. However, the impact on the ICER was considerable (increasing those for trastuzumab regimens to a range of £17,000-£25,000/QALY) when compared with the impact observed in GSK's original deterministic sensitivity analysis, which assumed a lower hazard ratio equal to that of capecitabine (ICERs ranged from dominant to around £7,000/QALY). This implies that the ERG used an extreme assumption that the efficacy of trastuzumab regimens is lower than that of capecitabine, i.e. trastuzumab impairs time to progression when compared with capecitabine. It is clear from the GBG 26 trial that trastuzumab in combination with capecitabine significantly improves time to progression when compared with capecitabine, and this efficacy is supported by evidence from a number of uncontrolled studies as described in section 1.2.2. Therefore we believe that in the absence of randomised controlled data our use of the weighted pooled estimate from uncontrolled trials provided a more robust assessment of trastuzumab efficacy than the extreme assumption applied by the ERG. Further, the availability of the GBG 26 study data allows for a comparison with randomised data, albeit indirectly. We therefore believe that GBG 26 provides the most robust estimate, and we have used these data in our updated analyses.	Comments noted. The Committee's interpretation of the cost effectiveness of lapatinib has been based on the revised analyses submitted by GSK. See FAD sections 3.15 to 3.17 and 4.8 to 4.15.

Consultee	Comment	Response
GSK	In order to address the Appraisal Committee's concerns about uncertainty around the above variables, we have run revised sensitivity analyses using the updated assumptions described above. Since these above revised assumptions affect only comparisons with trastuzumab-containing regimens the single agent chemotherapy comparisons have been excluded from the results (Table 2.2) for clarity. The ERG reports that trastuzumab monotherapy is rarely used in this setting, which is consistent with the recent market research data reported above. Therefore the trastuzumab monotherapy comparison is included for completeness, but is shaded in the table to allow focus on the most relevant comparator regimens – single agent chemotherapies and trastuzumab in combination with either capecitabine or vinorelbine. **Table 2.3. Scenario analyses using updated assumptions** ***(included but not reproduced here)***	Comments noted. The Committee's interpretation of the cost effectiveness of lapatinib has been based on the revised analyses submitted by GSK. See FAD sections 3.15 to 3.17 and 4.8 to 4.15.
GSK	These results show that in the new base case, lapatinib in combination with capecitabine remains a highly cost effective option when compared with the key trastuzumab-containing regimens. Probabilistic sensitivity analysis performed on Scenario 9 suggests that the likelihood of lapatinib plus capecitabine being cost effective in the £20,000-£30,000/QALY range is just over 60% when compared with trastuzumab plus capecitabine; the likelihood of being in this range when compared with trastuzumab plus vinorelbine is 78%-82% (see Appendix 5 for further details).	The Committee considered that the data provided by GSK demonstrated that the comparison of lapatinib with trastuzumab containing regimens was based on a comparison of capecitabine with trastuzumab containing regimens which was not cost effective. The Committee concluded that the result of the cost-effectiveness analysis for laptatinib versus trastuzumab was based on a comparison of trastuzumab versus capecitabine which was not cost effective and was therefore not supportable. See FAD section 4.13.

Consultee	Comment	Response
GSK	We recognise that, compared with capecitabine and vinorelbine monotherapies, lapatinib in combination with capecitabine is unlikely to be cost effective and therefore the current recommendations regarding these comparisons are reasonable. However we have significant concerns with the Committee's decision not to consider trastuzumab, in the context of its use beyond progression, as a relevant comparator. Whilst we accept some limitations of the original evidence base, collectively the updated body of evidence firmly establishes the use of trastuzumab beyond progression as the most common treatment approach for patients in this setting in the UK. The recently revised NICE methods guide states that unlicensed comparator technologies may be considered if they are used routinely in the NHS. We believe that disregarding the current evidence on clinical practice, continuing to disregard trastuzumab regimens as an important element of the comparator base, and non-consideration of emerging comparative clinical evidence confirming the efficacy trastuzumab in this setting, would result in provision of guidance to the NHS which is out-dated, incomplete and not reflective of current clinical practice. Having addressed the concerns regarding trastuzumab costs and incorporated the new evidence into the analysis, lapatinib in combination with capecitabine remains highly cost effective (dominant) when compared with the key trastuzumab-containing regimens used in these patients. We believe that lapatinib plus capecitabine should be recommended as a licensed and proven alternative treatment option, when trastuzumab is being considered for continuation beyond disease progression..	Comments noted, no actions required. The Committee considered that the data provided by GSK demonstrated that the comparison of lapatinib with trastuzumab containing regimens was based on a comparison of capecitabine with trastuzumab containing regimens which was not cost effective. The Committee concluded that the result of the cost-effectiveness analysis for laptatinib versus trastuzumab was based on a comparison of trastuzumab versus capecitabine which was not cost effective and was therefore not supportable. See FAD section 4.13.

Consultee	Comment	Response
GSK	Patients with ErbB2-positive advanced or metastatic breast cancer, who progress on or following treatment with trastuzumab, represent a population with an unmet clinical need and very few therapeutic options available to them other than trastuzumab, which is unlicensed for use in this setting. As metastatic breast cancer is essentially incurable, effective treatment options that can delay progression or extend survival without negatively impacting quality of life and adding unacceptably to the toxicity burden are greatly needed in this patient group. For these women, who are relatively young, with good performance status, the modest gains associated with medicines at this stage of breast cancer can be disproportionately valuable; we believe that the value of additional progression-free time at the end of a patient's life is not fully represented in a cost utility analysis.	The economic analysis has been completed in accordance with the NICE guide to the methods of technology appraisal with consideration of the benefits of progression free survival and overall survival. The Committee considered the wider benefits of treatment with lapatinib. It was not persuaded that the benefits associated with the mode of administration of lapatinib or the importance of patient choice should alter their decision about lapatinib being an appropriate use of NHS resources. In addition the Committee has considered the supplementary advice from the Institute to be taken into account when appraising treatments which may be life extending for patients with short life expectancy. See FAD sections 4.16 4.18 to 4.20.

Consultee	Comment	Response
GSK	Lapatinib plus capecitabine provides superior outcomes in terms of progression-free life years, life years and QALYs versus single agent chemotherapies. For patients who are more likely to be continued on a trastuzumab regimen beyond progression, lapatinib plus capecitabine is a clinically and cost-effective alternative, even when assumptions are amended to address the trastuzumab dosing and wastage issues identified by the ERG. In its original submission, GSK presented an argument that the subset of patients that is more likely to receive treatment with trastuzumab beyond progression includes patients with progression at an isolated site, patients with few metastases in the soft tissues or bone, and patients who experienced a previous good response to trastuzumab. However, we acknowledge such an approach presents a number of challenges: • The difficulty in creating clear and unambiguous clinical criteria with which to define such a subgroup creates potential equity issues – a view that has been confirmed by UK medical oncologists • Equity issues may be compounded by the inability to identify whether such subgroups are associated with differential effectiveness. The only randomised trial to demonstrate the effectiveness of trastuzumab used beyond progression (GBG 26) included a broad population of patients that had received one prior line of trastuzumab therapy, rather than a selected subgroup. In addition the pivotal lapatinib study also included a broader group of patients consistent with the license.	Comments noted. The Committee considered that there was currently insufficient evidence to recommend lapatinib in any specific subgroups of patients. See FAD section 4.17.

Consultee	Comment	Response
GSK	GSK strongly believes that lapatinib offers tangible benefits to the group of patients within its licensed indications which has limited treatment options. GSK is committed to a solution that ensures access to lapatinib for all patients with the potential to benefit within its licensed indication. To this end, we have performed an analysis to demonstrate the overall cost effectiveness of lapatinib plus capecitabine against the three major existing therapeutic options currently employed within the NHS (capecitabine monotherapy, and trastuzumab in combination with capecitabine or vinorelbine).	The Committee has considered the blended comparator, including the application of the patient access scheme to the blended comparator. The Committee was not persuaded that it was appropriate to mix together independent health technologies to produce a single estimate representing the cost effectiveness of lapatinib in comparison with 'standard care'. See FAD sections 3.17 to 3.19 and 4.13 to 4.15.
GSK	Using the revised "base case", as described above (Scenario 9), GSK has generated a cost effectiveness estimate for lapatinib plus capecitabine compared with a 'blended' comparator consisting of a weighted average of both the costs and effectiveness of the three key treatment options. To ensure that all patients, including those receiving less commonly used interventions identified in the IMS Oncology Analyzer study described above (Table 1.1) were represented in the analysis, the less common treatment regimens were re-allocated to the three key intervention groups (see Appendix 1 for methodology), generating final proportions of: • 44% capecitabine monotherapy • 27% trastuzumab in combination with vinorelbine • 29% trastuzumab in combination with capecitabine The results of the blended analysis are presented in Table 4.1 below. **Table 4.1 Overall cost effectiveness of lapatinib in combination with capecitabine** ***(included but not reproduced here)***	The Committee has considered the blended comparator, including the application of the patient access scheme to the blended comparator. The Committee was not persuaded that it was appropriate to mix together independent health technologies to produce a single estimate representing the cost effectiveness of lapatinib in comparison with 'standard care'. See FAD sections 3.17 to 3.19 and 4.13 to 4.15.

Consultee	Comment	Response
GSK	These results show that, using the original (Scenario 3) and the updated clinical data (Scenario 6), with GSK's original assumptions regarding wastage and dosing schedule for trastuzumab, incremental cost effectiveness ratios for lapatinib plus capecitabine are £30,474/QALY (Scenario 3) and £23,463/QALY (Scenario 6), when compared with a 'blended' comparator base broadly representing current clinical practice. However, in addressing uncertainties raised in the ACD it is clear that issues such as drug wastage and dosing schedules for trastuzumab have an impact on the cost effectiveness results, and this is reflected in the higher ICER of around £61,000 when these are taken into account in the blended comparator analysis (Scenario 9). In recognition of the need to address the risks associated with these uncertainties, and to demonstrate clearly the value that lapatinib offers the NHS, GSK proposes an access programme for lapatinib that will reduce the cost per QALY to a level which is within acceptable limits. The programme aims to facilitate equitable patient access to treatment and maximise value to the NHS by linking payment to clinical benefit. This scheme will be outlined in an addendum to this response. **Response to ERG report included but not reproduced** **Appendices to the ACD response included but not reproduced** **Addendum to the ACD response included but not reproduced**	The Committee has considered the blended comparator, including the application of the patient access scheme to the blended comparator. The Committee was not persuaded that it was appropriate to mix together independent health technologies to produce a single estimate representing the cost effectiveness of lapatinib in comparison with 'standard care'. See FAD sections 3.17 to 3.19 and 4.13 to 4.15.
Joint response: Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care, and Macmillan Cancer Support	We are disappointed that the Appraisal Committee is unable to recommend Lapatinib (in combination with capecitabine) for the routine treatment of women with advanced or metastatic breast cancer whose tumours overexpress HER2. However, we acknowledge that there needs to be further robust evidence and welcome the committee's proposal for research comparing lapatinib plus capecitabine with trastuzumab-containing regimens and other chemotherapy regimens used in the advanced or metastatic setting after progression with trastuzumab. We also welcome the call for further research to have a particular emphasis on identifying potential subgroups who may particularly benefit from lapatinib.	Comments noted, see responses below.

Consultee	Comment	Response
Joint response: Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care, and Macmillan Cancer Support	**Do you consider that all of the relevant evidence has been taken into account?** As noted in the Appraisal Consultation Document, we acknowledge that there are issues surrounding insufficient evidence and uncertainties in the data, in particular with regards to the comparators. We welcome consideration of the patient perspective on acceptance of side effects by people at this stage of disease and would like to see more qualitative evidence regarding patient perspective taken into account for outcome measures. We would like to see further consideration of the advantages lapatinib could provide in terms of its administration. Patients with metastatic breast cancer commonly have limited treatment options and lapatinib is particularly advantageous as it is administered orally as a tablet. This treatment therefore offers significant benefits to patients' quality of life and does not result in additional hospital visits that may occur with alternative treatment regimens, providing the patient with valuable extra time to spend with friends and family. Administration by tablet form also reduces NHS costs of treatment provision as well as patient costs associated with attending hospital such as parking, travel, time off work and child care. Although non-NHS/PSS costs are not within the perspective the Secretary of State gives to NICE, we believe that these are important factors for the Appraisal Committee to consider.	Comments noted. The Committee considered the wider benefits of treatment with lapatinib, as well as the importance of patient choice and availability of treatments of with oral administration. In addition the Committee has considered the supplementary advice from the Institute to be taken into account when appraising treatments which may be life extending for patients with short life expectancy. See FAD sections 4.16 and 4.18 to 4.20.

Consultee	Comment	Response
Joint response: Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care, and Macmillan Cancer Support	**Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate?** We share the Appraisal Committee's concern about the pooling of estimates from non-RCT and observational studies. However, there is evidence to show that lapatinib would be an effective treatment option for some patients with metastatic breast cancer as there was a statistically significant improvement in the time to progression and the progression-free survival when compared with capecitabine monotherapy. Evidence suggests that the potential side effects of lapatinib can be controlled resulting in a relatively high quality of life without a reduction in clinical effectiveness. For people with metastatic breast cancer the importance of this should not be underestimated. Furthermore, as noted in the Appraisal Consultation Document, people at this stage of disease are often willing to accept side effects in order to have the benefits of treatment. We acknowledge that the evidence to support the clinical effectiveness of lapatinib for patients with (or at a high risk of developing) brain metastases is currently unclear. We welcome the EMEA request to have lapatinib-containing therapy further investigated as a beneficial treatment for this sub-group, as patients who develop brain metastases often experience a negative impact on their quality of life.	Comments noted. The Committee recognised that lapatinib may offer benefits in progression free survival and that adverse events associated with treatment with lapatinib could be appropriately managed. See FAD sections 4.5 and 4.6. However, for both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations (Social Value Judgements - Principles for the development of NICE guidance; principle 2).

Consultee	Comment	Response
Joint submission: Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care, and Macmillan Cancer Support	**Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS?** It is disappointing to note that the committee is not able to recommend lapatinib (in combination with capecitabine) for the routine treatment of women with advanced or metastatic breast cancer whose tumours overexpress HER2. As patient organisations, we would like to emphasise how important it is to offer patients greater treatment choice. We support NICE's recommendation that further work needs to be done to clarify the optimum treatment for those whose disease has progressed following treatment on anthracyclines, taxanes and trastuzumab. Laptinib (with capecitabine) could be an alternative as it targets both the Erb1 and Erb2 receptors. However, to inform what should be regarded as a standard treatment pathway there needs to be evidence comparing this with trastuzumab-containing regimens and other chemotherapy regimens so that clear guidance can be given to clinicians to eliminate the variation that currently exists. We also welcome the recommendation that in this further research emphasis should be placed on identifying potential subgroups (such as those with brain metastases) who could particularly benefit from this treatment. We also note that research is being carried out to improve the methods of accurately detecting those patients who will benefit from HER2 (Erb2) receptor targeted treatments. These cancers are often more aggressive and the prognosis for these patients is typically poor. Targeted treatments for these cancers are needed to ensure that we improve the quality of life and survival for this group of patients.	Comments noted, no actions required.

Consultee	Comment	Response
Joint submission: Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care, and Macmillan Cancer Support	**Are there any equality related issues that need special consideration that are not covered in the ACD?** The recent NICE Citizens Council report into QALYs and the severity of illness recommends that NICE and its advisory bodies should take the severity of a disease into account when making decisions. We would like to see, in the 'consideration of the evidence' section, whether the Appraisal Committee was persuaded in this instance to take the severity of this condition into consideration alongside the cost and clinical effectiveness evidence.	The Committee has considered the supplementary advice from the Institute to be taken into account when appraising treatments which may be life extending for patients with short life expectancy. See FAD sections 4.18 to 4.20.
Royal College of Nursing	**Appraisal Consultation Document – RCN Response** The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Lapatinib for the treatment of previously treated women with advanced, metastatic or recurrent breast cancer. Nurses working in this area of health have reviewed this document. We note that this health technology is not recommended of the routine treatment of women with advanced or metastatic breast cancer whose tumours over-express HER2 except in the context of clinical trials. This will obviously be disappointing news for this group of patients.	Comments noted, no actions required.

Consultee	Comment	Response
Royal College of Physicians	The oncology community as represented by the Royal College of Physicians, the Royal College of Radiologists, the Joint Collegiate Council for Clinical Oncology, the Association of Cancer Physicians and the NCRI Breast Group (who coordinated this response) are grateful for the opportunity to consider the ACD for the above subject. We would like to make the following comments: Lapatinib is licensed in Europe for the treatment of metastatic breast cancer expressing the growth factor receptor HER2 following progression during or after treatment with trastuzumab. Significantly improved time to progression (the pre-specified primary endpoint) was reported, with minimal excess toxicity over and above capecitabine alone. The trial was underpowered to determine any difference in overall survival and the survival analysis is confounded by crossover to lapatinib in the capecitabine arm alone, a treatment recommendation that was made by the Independent Data Monitoring Committee due to the very clear effects of the study drug on the underlying disease. At the time the study was conducted the standard of care was chemotherapy alone, and the choice of single agent capecitabine as the comparator was appropriate and consistent with UK practice. However, the standard of care is changing as data emerges to show that continued inhibition of HER2 with trastuzumab is also superior to chemotherapy with capecitabine alone (von Minckwitz et al. GBG-26 study, ASCO Proceedings 2008). Although there is not regulatory approval for trastuzumab beyond progression, it is frequently and increasingly used in many centres throughout the UK.	Comments noted The Committee recognised that lapatinib may offer benefits in progression free survival. However, for both legal and bioethical reasons those undertaking technology appraisals and developing clinical guidelines must take account of economic considerations (Social Value Judgements - Principles for the development of NICE guidance; principle 2). See FAD section 4.5. The Committee has considered the evidence about the proportion of people continuing trastuzumab following progression of disease. See FAD sections 3.14, 4.2 and 4.3.
Patient Expert	As one of the patient experts nominated by Breast Cancer Care I would like to echo the comments made in the joint statement issued by this organisation together with Breakthrough Breast Cancer, Breast Cancer Campaign and Macmillan Cancer Support (merged with Cancerbackup in April 2008). Whilst the outcome of this appraisal is disappointing, I recognise that for this small but significant group of patients any treatment option should be proven to be safe, effective and well evidenced. It is encouraging to see that further research is proposed including the identification of potential subgroups that may benefit from lapatinib, in particular the evaluation of the incidence of brain metastases.	Comments noted, see response to the joint response from Breakthrough Breast Cancer, Breast Cancer Campaign and Macmillan Cancer Support.

Comments received from commentators

Commentator	Comment	Response
Roche Products	**a) Clinical effectiveness of trastuzumab in 2nd line metastatic breast cancer patients** A randomized control trial has now reported results comparing Trastuzumab+Capecitabine with Capecitabine monotherapy in 156 patients with HER-2 positive metastatic breast cancer following progression with trastuzumab treatment. The data from the GBG-26 study was recently presented in a poster at the 44th ASCO Annual Meeting 2008 by *Von Minckwitz* et.al (2008). The OS and TTP results reported in this study provide a more robust evaluation of the efficacy of trastuzumab compared to the pooled non-RCT study results previously considered by the appraisal committee. The pooled analysis of eight non-RCT Trastuzumab-based studies presented within the manufacturer submission reported a weighted TTP median of 21.8 weeks for trastuzumab. The recent GBG-26 RCT illustrates that the Trastuzumab+Capecitabine combination therapy median TTP was 35.5 weeks (8.2 months). The TTP Hazard Ratio reported in this study for trastuzumab was 0.69 (two-sided p=0.034; one-sided p=0.017). The trastuzumab arm within the GBG-26 demonstrated an additional 5.1 months overall survival with a HR=0.76 (two-sided p=0.26; one-sided p=0.13), although this is not yet statistically significant. **Table 1: Comparison of hazard ratios from GBG-26 and EGF100151 studies**. ***(included but not reproduced here)***	The results of the GBG26 trial have been considered by the Committee and are summarised in the FAD and. See FAD sections 3.5, 4.4 and 4.11.
Roche Products	The above efficacy data provides strong evidence to question the assumption and conclusion within the manufacturer's submission that lapatinib is more clinically effective when compared to trastuzumab. The above analysis in fact suggests the opposite, with trastuzumab demonstrating a larger treatment effect over the common comparator capecitabine, when compared to the most recent follow-up data for lapatinib.	The results of the GBG26 trial have been considered by the Committee and are summarised in the FAD and. See FAD sections 3.5, 4.4 and 4.11.

Commentator	Comment	Response
Roche Products	**Validity of trastuzumab as a comparator technology** Roche believe that trastuzumab is not a relevant comparator in the relapsed metastatic breast cancer setting following prior treatment with trastuzumab. This is for the following 2 reasons: a) Trastuzumab accounts for a small share of current treatment within the specific population of interest, as substantiated by clinicians in section 4.9 of the ACD. b) Trastuzumab is not included as a relevant comparator within the final scope for the appraisal, developed following consultation and a scoping workshop Roche has recently commissioned a substantial piece of market research data[1] of 222 patient records covering 33 of the Cancer Networks within the UK. All 222 patients were previously treated with trastuzumab in the metastatic setting and their subsequent treatment following progression captured. The analysis reported that of the 222 HER 2 patients evaluated, who received trastuzumab in the first line metastatic breast cancer setting; only 26 patients (12%) received trastuzumab following disease progression. This analysis confirms the clinical testimony presented to the appraisal committee, that trastuzumab within the population of interest for this evaluation is not standard of care within the NHS. At present with a high degree of certainty, lapatinib has failed to demonstrate cost effectiveness compared to both capecitabine and vinorelbine. Therefore to demonstrate the cost effectiveness of lapatinib compared to trastuzumab is of limited relevance given the stated efficiency objectives of NICE. If positive guidance were published for lapatinib on the basis it demonstrated cost effectiveness compared to trastuzumab, it would lead to the possibility of lapatinib being potentially utilised when 2 more cost-effective alternative treatments were available (xeloda and vinorelbine).	The Committee has specifically considered the use of trastuzumab after progression of disease. It was persuaded by the evidence submitted and the testimony from the clinical specialists that it should consider the clinical- and cost-effectiveness analyses that included trastuzumab as a comparator. See FAD sections 3.14, 4.2 and 4.3.

[1] Herceptin Patient Case Record Research, Double Helix Development, June 2008

Commentator	Comment	Response
Roche Products	**b) Price of Lapatinib** The price of Lapatinib used in the base-case cost effectiveness calculations within the manufacturer's submission do not appear consistent with the latest unit cost of Lapatinib reported[2]. In the base case scenario the price of one Lapatinib tablet is assumed to be £11.00. The price of Lapatinib reported is £804.30 per 70 tablets meaning that each tablet costs £11.49, as confirmed in section 2.3 of the ACD. The difference in price per tablet translates to £2.45 additional cost per day of treatment which in turn translates to £894.25 additional cost for every year of treatment. Although a variation in price for each Lapatinib tablet has been considered in scenario 1[3], the impact of the additional cost for each day of treatment has not been accurately reflected within the base case estimates of the cost effectiveness of lapatinib. **c) Lapatinib phase III RCT follow-up period** Roche believe the clinical effectiveness of lapatinib has been overestimated in the cost-effectiveness calculations through the application of less mature clinical trial data from the lapatinib phase III RCT. Roche would highlight to the Committee that a more recent follow-up of the lapatinib phase III clinical data is available (September 2007 compared to April 2006). The September 2007 follow-up illustrates that the treatment effect of lapatinib compared to capecitabine is not as large when compared to the earlier less mature follow-up data utilised in the cost effectiveness calculations for both the TTP and OS endpoints. **Table 2: Comparison of efficacy by follow-up in EGF100151** ***(included but not reproduced here)*** The hazard ratio of the overall survival currently used in the effectiveness calculations is 0.78 (95% CI 0.55 to 1.12; p=0.177). The hazard ratio calculated using the longer follow-up data is 0.90 (95% CI 0.71 to 1.12; p=0.3). Likewise the TTP hazard ratio demonstrates a reduced treatment effect in the longer follow-up data for lapatinib, increasing from 0.57 to 0.72.	The lapatinib list price was used in the revised economic analyses provided by the manufacturer. The Committee's interpretation of the cost effectiveness of lapatinib has been based on these revised analyses. See FAD sections 3.15 to 3.17 and 4.8 to 4.15. The revised economic analyses included updated survival data (hazard ratio 0.90). The manufacturer of lapatinib confirmed that there is no updated time to progression data. Differences in the estimates of time to progression are because of differences in the investigator and independent data committee assessments (hazard ratios 0.57 and 0.72). See the GSK response to the report produced by the DSU.

[2] National electronic Library for Medicines
[3] Manufacturer's Submission

Commentator	Comment	Response
Roche Products	**Comparative cardio-toxicity of lapatinib and trastuzumab** Roche considers the following statement in section 4.5 of the ACD an unfair representation of the available clinical evidence: *"The committee agreed that the currently available evidence suggests that cardio-toxicity was less of a problem with lapatinib treatment"*. The statement fails to give adequate consideration or necessary qualification relating to the confounding effect of patient inclusion criteria within the relevant studies. The EGF100151 screened out many patients with the potential to develop HER2 related cardiac dysfunction due to the requirement for previous trastuzumab therapy and the additional inclusion criteria within the EGF100151 study for LVEF to be within the institution's normal range i.e. patients with pre-existing heart disease are excluded. Consequently to compare the cardio-toxicity outcomes naively across studies performed in 2 different populations / lines of therapy is not a fair representation of the comparative side effect profile of the two interventions. **e) 3-weekly trastuzumab drug administration schedule** An audit of 1064 electronic case assessment forms in 2007 covering all Cancer networks[4] provided evidence that 98% of first line and 92% of second line metastatic breast cancer patients receiving trastuzumab received a 3-weekly drug administration schedule. This evidence supports the expert testimony presented to the committee that a 3-weekly regimen is standard of care within the UK and the most appropriate assumption to inform any economic evaluation.	This has been amended in the FAD. The Committee considered the administration schedule for trastuzumab. See FAD section 4.12.
Roche Products	**Correct recommendation following evaluation of multiple comparators** Based on the analysis of available evidence we believe the recommendations within the ACD are appropriate. Firstly a comparison of trastuzumab with lapatinib is not relevant given the available evidence of current treatment practice within the NHS. Secondly even if the comparison was considered a valid decision problem, the available evidence suggests that such an economic evaluation would simply determine the 3rd or 4th ranked cost effective treatment when including Xeloda and vinorelbine as relevant comparators.	Comments noted, no actions required.

[4] Breast Cancer Patient level Study Wave 5, Genactis, Roche data on file, 2007

Commentator	Comment	Response
Southampton Health Technology Assessment Consortium	Do you consider that all of the relevant evidence has been taken into account? YES Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence, and that the preliminary views on the resource impact and implications for the NHS are appropriate? YES Do you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS? YES Are there any equality related issues that need special consideration that are not covered in the ACD? NO We have the following additional comment: one of the bullet points under 3.11 is confusing by using commas for decimals in currency i.e. separating pounds from pence (see below) - suggest replacing with full stops "The cost for administering chemotherapy infusion for trastuzumab changed from £207,22 per infusion used in the manufacturer submission to £117,00 per infusion based on a published assessment report for a previous appraisal."	Comments noted, no actions required. This has been amended in the FAD.

Comments received from members of the public

Role*	Comment	Response
Pharmaceuticals manufacturer	**NICE consultation – Appraisal Consultation Document – Lapatinib for the treatment of previously treated women with advanced, metastatic or recurrent breast cancer** Thank you for your letter of 30th June 2008 requesting comments on the ACD and evaluation report of the above Technology Appraisal. [redacted] have no comments at this time but are grateful for the opportunity to comment on this appraisal. Should you require any further clarification please feel free to contact me.	Comments noted, no actions required.

Organisations stating that they had no comments:

National Collaborating Centre for Cancer

Department of Health

Royal College of Pathologists

Summary of comments received from members of the public

Theme	Response
No responses received	n/a

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.