NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Lapatinib for women with previously treated metastatic breast cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD 2)

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
GSK	**1. Do you consider that all of the relevant evidence has been taken into account?** The current ACD presents the data clearly, and broadly reflects the relevant evidence. However, we are concerned that evidence supporting the level of continued use of trastuzumab beyond progression, as well as new market research advising on the most appropriate estimates of intravenous medication wastage and three weekly trastuzumab use, have not been comprehensively taken into account: *1.1. Evidence for trastuzumab use in current clinical practice* The Committee notes inconsistency in the market research provided to support the level of trastuzumab use beyond progression in clinical practice (Section 4.2), quoting a range of 10% to 50% of patients receiving this treatment. Whilst the Committee accepted that the higher estimates were likely to be the more appropriate (as suggested by the recent, independently collected IMS data submitted in our response to the first ACD, and confirmed by NICE-nominated clinical specialists), the ACD continues to use the 12% figure in sensitivity analyses. This figure was proposed by the manufacturer of trastuzumab, but was rejected as an unrealistic estimate by the specialists at the 18 September 08 Appraisal Committee meeting; it has also been highlighted that there is no information on the methodology used to derive it. Furthermore, the Royal College of Physicians in their feedback on the first ACD[1] confirmed that the standard of care is changing as data emerges to support the strategy of continued ErbB2 suppression, and that trastuzumab is frequently and increasingly used beyond progression in many centres throughout the UK.	Comments noted, see responses 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. The DSU provided an estimate of cost effectiveness using an assumption that the proportion of people having trastuzumab following progression of disease was 12%; this is included in the evidence section of the FAD as it was considered by the Committee. The Committee noted the range of estimates of continued trastuzumab use following 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	Further interrogation of the independently collected IMS dataset, which was considered by clinical experts at the Appraisal Committee meeting as the more robust data source, confirms that trastuzumab has been consistently used over several years in the majority of patients whose disease has progressed after receiving trastuzumab (Table 1). **Table 1. Trastuzumab use beyond progression – IMS market research data** ***(included but not reproduced here)***	The Committee has specifically considered the use of trastuzumab following 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	In continuing to employ the lowest estimate of trastuzumab use beyond progression we believe that the DSU/Committee has failed to take into account fully the evidence from clinical experts, the lack of methodological detail in how the lower estimate was obtained, and the comprehensive reports of market research (including methodology) provided by GSK. We therefore believe that £63,034/QALY (Section 4.14 of the ACD) is an unrealistic and misleading representation of the cost effectiveness of lapatinib in combination with capecitabine, in the context of the Lapatinib Patient Access Programme (LPAP), and that the more relevant range would be a maximum of £26,993 per QALY gained (at the lower estimate of 49% use) and as low as £16,387 if a figure of 56% is used. In addition, given the publication of the GBG-26 study (von Minckwitz et al)[2] and the resulting evidence of the clinical validity of this treatment approach, the unlicensed use of trastuzumab regimens in this indication may actually increase further. In these circumstances the Lapatinib Patient Access Programme would provide an even more cost effective use of NHS resources than those presented above.	The DSU provided an estimate of cost effectiveness using an assumption that the proportion of people having trastuzumab following progression of disease was 12%; this is included in the evidence section of the FAD as it was considered by the Committee. The Committee noted the range of estimates of continued trastuzumab use following 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. The Committee has considered the patient access scheme and its application to the blended comparator. The FAD considerations no longer refer to the ICER of £63,034. See FAD sections 4.14 and 4.15.

Consultee	Comment	Response
GSK	*1.2. Consideration of evidence underlying assumptions on trastuzumab wastage and administration* In the original ACD, concerns were raised as to the appropriate assumptions for the extent of wastage for intravenous therapies, the extent to which trastuzumab is given three-weekly, and that the cost effectiveness estimates were sensitive to these assumptions. As a result GSK undertook a survey of 24 oncology pharmacists from 17 cancer networks to understand the most appropriate assumptions to be used in the analysis. The mean results from this research were the basis of the assumptions used within the revised cost effectiveness analysis, and were presented along with the methodology used in our response to the ACD. The results of this research are not referred to in the ACD and clinical opinion is used to justify the consideration that the estimates for the costs of trastuzumab treatment may still be over estimated. We accept that our research shows that in some centres this would be the case. However as means were used, the results of the research also demonstrate that in some centres these figures were likely to be underestimates. We believe that in reaching its conclusions the Committee should also give consideration of the impact of these alternative assumptions that would result in improved cost effectiveness for lapatinib.	The FAD describes the survey undertaken by GSK. See FAD section 3.15. 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	*1.3. Lack of consideration of the Lapatinib Patient Access Programme (LPAP)* Very minimal consideration appears to have been given to the Lapatinib Patient Access Programme *per se*. We would like to reinforce that the programme has been designed to be consistent with current clinical practice and NHS financial flows to aid implementation in the NHS. It also allows all eligible patients to receive up to the first 12 weeks of treatment free meaning that in general terms the NHS does not pay for those patients who do least well on lapatinib. The programme also allows equitable access for all patients to lapatinib whereas currently, although widespread, the use of trastuzumab beyond progression is variable.	The Department of Health considers the appropriateness of patient access schemes for use in the NHS. The Committee considered the application of the patient access scheme to both the individual comparators and the blended comparator. The Committee did not consider that application of the patient access scheme to the blended comparator was appropriate because of the limitations associated with the blended comparator. The Committee did not consider that the patient access scheme when applied to capecitabine and vinorelbine monotherapies provided a cost effective use of NHS resources. See FAD sections 4.10 and 4.15.
GSK	**2. 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?** As acknowledged in our previous comments on the first ACD, we consider the interpretation of the pivotal clinical trial EGF100151 is reasonable, as well as the interpretation of the cost effectiveness of lapatinib plus capecitabine versus single-agent chemotherapies. However, we have significant concerns about the interpretation of the cost effectiveness evidence versus trastuzumab-containing regimens submitted by GSK. Whilst we agree with the Committee's conclusion that the standard of treatment could include capecitabine, vinorelbine, and trastuzumab-containing regimens (Section 4.2), we are very concerned about the Committee's consideration of trastuzumab regimens within the appraisal. Our concerns are several-fold, and are discussed below:	Comments noted, see responses below.

Consultee	Comment	Response
GSK	*2.1. Definition of standard treatment for patients whose disease progresses after receiving trastuzumab in the metastatic setting* We welcome the Committee's acceptance that trastuzumab regimens are included in the range of treatments given in usual clinical practice in this patient population, and acknowledge that this practice is variable despite its ubiquity. In our response to the first ACD we specifically addressed the issue of variability in standard clinical practice by including the costs and effects of the different options in a single 'usual practice' comparator arm (the 'blended' analysis). To define the average levels of different interventions used in usual clinical practice, we interrogated IMS patient note level data, commissioned and collected independently of GSK, and this was backed up with physician-based market research commissioned to answer this question. The results have since been endorsed by the clinical community, not least at the September 2008 Appraisal Committee meeting. GSK's 'usual practice' comparator approach has been rejected by the DSU and Appraisal Committee in favour of an alternative methodology which, in effect, assumes that the lapatinib regimen would replace only the least costly intervention used in clinical practice, and more costly interventions would cease to be used. This is unrealistic in the context of a Single Technology Appraisal (STA), does not reflect the realistic opportunity cost to the NHS of comparisons with current practice, and is discussed further below. We assert that the blended comparator is a more accurate reflection of average standard practice that would be displaced by the introduction of lapatinib in combination with capecitabine.	The Committee did not consider that it was methodologically appropriate to mix together mutually exclusive health technology programmes to produce a single ICER representing the cost effectiveness of lapatinib in comparison with 'usual practice'. See FAD section 4.14. The incremental analysis by the DSU is an alternative presentation of data that GSK used to determine the estimates of incremental cost effectiveness of lapatinib against each individual comparator in their submission. Presenting data in this way is not unrealistic in the context of the STA or MTA where it is expected that manufacturers will demonstrate whether their technology is cost effective against a range of individual technologies currently in use in the NHS. The guide to the methods of technology appraisal is applicable to both the STA and MTA processes and ensures that the Committee applies the same decision rules irrespective of the process followed. The blended comparator obscures the result that lapatinib is not a cost effective alternative to capecitabine and vinorelbine and that displacing these technologies with lapatinib would result in an inefficient use of NHS resources. It does not therefore form an appropriate basis for decision making. See FAD sections 4.13, 4.14 and 4.15.

Consultee	Comment	Response
GSK	We would also like to respond to Section 4.3 of the ACD, which states that the Committee was mindful that allowing unlicensed comparators to be considered (2008 methodological guidance)[3] was intended 'to reflect the inclusion of technologies used routinely on the basis of clinical experience for many years and for which a licence had not therefore been requested'. This caveat is not explicitly stated in the methodological guidance, and appears to be a post hoc interpretation of the guidance. We therefore believe this should not be a factor for the Committee to consider. Both the 2008[3] and 2004[4] methods guides are very clear that both routine and best practice should be considered, that there will often be more than one relevant comparator technology because routine practice may vary across the NHS, and because best alternative care may differ from routine NHS practice. In conclusion the most reliable data sources suggest that the use of trastuzumab beyond progression is the most commonly used treatment strategy in these patients and therefore should be considered as a valid comparator for this appraisal.	This has been amended in the FAD. See FAD section 4.3. 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	*2.2. Consideration by the DSU of all treatment options in a single incremental analysis* We argue that our approach to the economic analysis, using a composite comparator representing standard practice in England and Wales, addresses the STA decision problem more appropriately than the consideration of all options in a single incremental analysis comparing each successive treatment from the least costly to the most. The STA decision problem, by definition, focuses on the evaluation of the economic impact of introducing a single intervention into clinical practice; the interventions that it will displace are not being appraised *per se*, and as such, any conclusions drawn on their cost effectiveness are unlikely to be implementable. The incremental approach adopted by the DSU and considered by the Committee is more suitable for an MTA, where several options are being assessed alongside each other to determine which should, and should not, be used on the NHS.	The incremental analysis by the DSU is an alternative presentation of data that GSK used to determine the estimates of incremental cost effectiveness of lapatinib against each individual comparator in their submission. Presenting data in this way is not unrealistic in the context of the STA or MTA where it is expected that manufacturers will demonstrate whether their technology is cost effective against a range of individual technologies currently in use in the NHS. The guide to the methods of technology appraisal is applicable to both the STA and MTA processes and ensures that the Committee applies the same decision rules irrespective of the process followed. The blended comparator obscures the result that lapatinib is not a cost effective alternative to capecitabine and vinorelbine and that displacing these technologies with lapatinib would result in an inefficient use of NHS resources. It does not therefore form an appropriate basis for decision making. See FAD sections 4.13, 4.14 and 4.15.

Consultee	Comment	Response
GSK	The single incremental analysis employed by the DSU is only one of several methodologies that might be used to evaluate the cost effectiveness of an intervention, and is not explicitly recommended in the methods guide. In considering the interpretation of the evidence provided, GSK's approach is consistent with the 2004 methodological guidance[4] (Section 1.4.1) which states that technologies can be considered cost effective if their health benefits are greater than their opportunity cost in terms of the health benefits associated with *programmes* that may be displaced to fund the new technology. In this case the programme that would be displaced by introducing lapatinib would consist of combination trastuzumab regimens (predominantly), as well as single-agent capecitabine. As discussed in our original submission, patients who receive trastuzumab beyond progression are those in whom the drug still appears to be having an effect, although we recognise that other factors such as local policy may also impact. Therefore whilst there is no evidence to confirm whether these interventions would be replaced at differential rates, there may be an increased clinical rationale for replacing trastuzumab, particularly when lapatinib is given as part of the proposed Lapatinib Patient Access Programme, as this would result in direct cost savings to the NHS. This would only serve to increase the relevance of trastuzumab-containing regimens within the comparator base, and to improve the relative cost effectiveness of lapatinib in combination with capecitabine versus usual practice.	The Committee did not consider that it was methodologically appropriate to mix together mutually exclusive health technology programmes to produce a single ICER representing the cost effectiveness of lapatinib in comparison with 'usual practice'. The incremental analysis by the DSU is an alternative presentation of data that GSK used to determine the estimates of incremental cost effectiveness of lapatinib against each individual comparator in their submission. Presenting data in this way is not unrealistic in the context of the STA or MTA where it is expected that manufacturers will demonstrate whether their technology is cost effective against a range of individual technologies currently in use in the NHS. The guide to the methods of technology appraisal is applicable to both the STA and MTA processes and ensures that the Committee applies the same decision rules irrespective of the process followed. The blended comparator obscures the result that lapatinib is not a cost effective alternative to capecitabine and vinorelbine and that displacing these technologies with lapatinib would result in an inefficient use of NHS resources. It does not therefore form an appropriate basis for decision making. See FAD sections 4.13, 4.14 and 4.15.

Consultee	Comment	Response
GSK	Furthermore, to insist that the comparator itself must be cost effective is inconsistent with the methodological guidelines,[3,4] which explicitly state that consideration should be given to routine and best practice in the NHS, that there will often be more than one relevant comparator because of variability in routine practice, and because routine practice may differ from best alternative care. The guidance does not state that in order to be considered, routine practice should be cost effective *per se*, and this is reflected in the current guidance for imatinib in chronic myeloid leukaemia[5] where an Appraisal Committee has approved an intervention on the basis of its cost effectiveness versus a cost-ineffective comparator. Indeed, the previous ACD, which acknowledged the cost effectiveness of lapatinib plus capecitabine versus trastuzumab-containing regimens in the base case, did not raise the lack of cost effectiveness of trastuzumab regimens *per se* as an issue, which implies that this is not a standard decision criterion for the Committee. In conclusion, we believe that the methodology that GSK employed provided a suitable interpretation of the cost effectiveness evidence for lapatinib in combination with capecitabine in comparison with the programmes of care likely to be displaced by its introduction.	The NICE guide to methods of technology appraisals indicates that *consideration* will be given to routine and best practice (section 2.2.3.1). The Committee has considered both routine and best practice. See FAD section 4.2 and 4.3. The methods guide does not make a judgement on the requirement for comparators to be cost effective. The judgement of the Committee on this issue is not therefore inconsistent with the methods guide. In the first ACD the Committee was not fully persuaded as to the extent that trastuzumab was in use in the NHS. It was not persuaded that the trastuzumab analyses should be taken into consideration in the decision making. Further evidence from the consultation on the first ACD meant that the Committee accepted that the trastuzumab analyses should be considered, but it was not persuaded that they formed an appropriate basis for deciding the cost effectiveness of lapatinib, because the data provided by GSK demonstrated that trastuzumab was in itself not cost effective in comparison with capecitabine. See FAD sections 4.3, 4.13.

Consultee	Comment	Response
GSK	*2.3. Interpretation of market research data, and its impact on cost effectiveness estimates* We are concerned that by including an estimate of 12% for trastuzumab beyond progression in a sensitivity analysis exploring the impact of varying the proportion of patients receiving trastuzumab, the DSU has given this estimate undue credence. No methodological detail for the market research has been provided, and as acknowledged by the Committee in Section 4.2 of the ACD the clinical specialist advisors considered the higher estimates (49%-56%) to be more appropriate. As mentioned in Section 1, IMS data shows that over the past three years trastuzumab has been used consistently in over half of patients whose disease has progressed after receiving trastuzumab (Table 1). We strongly believe that the IMS is the most reliable data source for the following reasons: IMS Oncology Analyzer uses a representative panel of hospitals; these hospitals are geographically varied and a minimum of 70% of all major cancer centres is included. IMS data is longitudinal enabling full patient history to be obtained since diagnosis, and is collected and analysed independently of the manufacturer. As a result end users of the data have no part in selecting participants, or in data collection or collation. The IMS and data set therefore represents a robust picture of prescribing behaviour from an independent source.	The DSU provided an independent report and included estimates of cost effectiveness where the proportion of people having trastuzumab following progression of disease was 12% these are included in the evidence section of the FAD as they represent a lower estimate provided by one stakeholder. The Committee noted the range of estimates of continued trastuzumab use following 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	We therefore believe that the sensitivity analysis including the range 49% to 56% is more representative of the likely proportion, and that at the lower level of 49% lapatinib in combination with capecitabine in the context of the Lapatinib Patient Access Programme still represents a cost effective use of resources, at around £27,000/QALY. In addition, the interpretation of the evidence with respect to assumptions on the wastage and administration of trastuzumab do not fully consider the impact on cost effectiveness. As discussed above, the assumptions in our analysis were mean estimates derived from market research data from 17 cancer networks. The DSU sensitivity analysis only considered conservative scenarios regarding wastage and three-weekly trastuzumab, resulting in a lower acquisition cost for trastuzumab. The data demonstrate that there are also UK centres where wastage is higher, and 3-weekly trastuzumab administration is lower, and we believe that the implications of these alternative scenarios should also be considered to provide a balanced reflection on the likely cost effectiveness of the lapatinib regimen.	The Committee noted the range of estimates of continued trastuzumab use following 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. 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 these costs may still be overestimated. See FAD section 4.12.

Consultee	Comment	Response
GSK	*2.4. Interpretation of the relative clinical effectiveness of lapatinib and trastuzumab regimens* We agree that there is uncertainty in the relative clinical effectiveness of lapatinib- and trastuzumab-containing regimens in this setting, due to a lack of head-to-head data, and the consequent need to use alternative methods of estimating relative effectiveness. However since the original ACD randomised trial evidence on the effectiveness of trastuzumab beyond progression has been published and allows a significantly more robust estimation of this than was previously possible. The primary analysis of lapatinib- versus trastuzumab-containing regimens presented in our response to the first ACD was based on hazard ratios derived from the results of study GBG-26, and suggested that trastuzumab regimens are marginally less effective than lapatinib in combination with capecitabine. The DSU critique of the methodology used to derive the relative hazard ratios is addressed in our response to the Evaluation Report, and we maintain robustly that our methodology was appropriate given the data available. A secondary analysis was conducted using an updated pooled estimate of mostly non-comparative studies, and was included in our ACD response for completeness, as this was the method used in the original submission. Indeed, as acknowledged by the DSU in the Evaluation Report, the primary result is supported by this secondary result. In these circumstances we support our position that the best estimate of relative effectiveness is that from the indirect analysis based on hazard ratios from study GBG-26, particularly as the results are supported by the alternative secondary analysis.	The Committee considered the clinical effectiveness of trastuzumab and concluded that although in the absence of head to head comparisons of lapatinib and trastuzumab regimens, the indirect estimate was associated with uncertainty, it formed an appropriate basis for considering the cost effectiveness estimates presented by the manufacturer. See FAD section 4.11.

Consultee	Comment	Response
GSK	**3. 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?** We acknowledge that, compared with single agent chemotherapies, lapatinib in combination with capecitabine is unlikely to be cost effective within NICE's current decision making framework, even in the context of the proposed Lapatinib Patient Access Programme. However, as indicated above, we have major concerns with the Committee's decision not to consider the overall cost effectiveness of lapatinib in relation to a composite comparator consisting of the major treatments used in current clinical practice, including trastuzumab regimens. Both the 2004 and 2008 guides to the methods of technology appraisal[3,4] state that standard decision rules should be followed in combining costs and QALYs, and these should reflect any situation where dominance or extended dominance exists. However, the methods guides also highlight the importance of constructing an analytical framework so that estimates of clinical and cost effectiveness can be made *that are relevant to the clinical decision-making context*. We strongly believe that an incremental analysis is not a valid methodology for determining whether introducing a single intervention, which will displace a range of alternatives used in current practice, is a cost effective use of NHS resources (as in STA). The 'blended' comparator described in our submission represents current clinical practice, and is more reflective of the opportunity cost of interventions that would be displaced by lapatinib and capecitabine. Relying on single-agent chemotherapy as the principal comparator therefore fails to account for the cost savings that would accrue from the displacement of trastuzumab-containing regimens which are likely to continue to be used in current clinical practice. It is also dependent on a complete change in current practice which, given the widespread use of trastuzumab in this setting, and the recent data that supports its clinical validity, is unlikely to be achievable in practice.	The Committee did not consider that it was methodologically appropriate to mix together mutually exclusive health technology programmes to produce a single ICER representing the cost effectiveness of lapatinib in comparison with 'usual practice'. In both the MTA and STA programmes is expected that manufacturers will demonstrate whether their technology is cost effective against a range of individual technologies currently in use in the NHS. The guide to the methods of technology appraisal is applicable to both the STA and MTA processes and ensures that the Committee applies the same decision rules irrespective of the process followed. The blended comparator obscures the result that lapatinib is not a cost effective alternative to capecitabine and vinorelbine and that displacing these technologies with lapatinib would result in an inefficient use of NHS resources. It does not therefore form an appropriate basis for decision making. See FAD section 4.13, 4.14 and 4.15. The Committee has considered all comparators included in the manufacturer's decision problem, it has not therefore relied on the analyses with single agent chemotherapies. The Committee accepted that the trastuzumab analyses should be considered, but it was not persuaded that they formed an appropriate basis for deciding the cost effectiveness of lapatinib, because the data provided by GSK demonstrated that trastuzumab was in itself not cost effective in comparison with capecitabine. See FAD sections 4.2, 4.3 and 4.13.

Consultee	Comment	Response
GSK	In their deliberations the Committee was mindful of the draft clinical guideline currently under consultation,[6] which provisionally recommends that people who are receiving treatment with trastuzumab should not continue trastuzumab at the time of disease progression outside the central nervous system. Clearly this guideline is still subject to consultation and therefore should not form the basis of what constitutes current clinical practice. Also, whilst this recommendation suggests that continuation with trastuzumab should not be part of standard practice in the future, the implementation of this aspect of the guideline would be challenging in light of the acceptance by the clinical community of the importance of continued ErbB2 suppression despite progression. This was indicated in the Royal College of Physician feedback on the first ACD, which highlighted the changing standard of care with the emergence of new data for ErbB2-suppressing agents such as lapatinib and trastuzumab. It is also interesting to note that the draft guideline does, by implication, allow those patients that have progressed only in the brain to continue to receive trastuzumab. Therefore in effect trastuzumab would, at least, constitute standard of care in this patient group. The current proposals if implemented would result in allowing the unlicensed use of trastuzumab to continue at a higher cost to the NHS whilst denying the same use of an alternative product within its product licence. In rejecting GSK's approach to the decision problem (the blended comparator analysis), we believe that the provisional recommendations are not sound, and that they will *de facto* result in less efficient use of NHS resources, through the continued use of an intervention that is more expensive than the predominant alternative, especially when the Lapatinib Patient Access Programme is applied.	The Committee considered that it was appropriate to be mindful of the recommendations from the NICE clinical guideline 81 on advanced breast cancer. The clinical guideline 81 recommends that treatment with trastuzumab should be discontinued at the time of disease progression outside the central nervous system. Treatment with trastuzumab is recommended to be continued only if disease progression is solely within the central nervous system. The Committee did not consider that it was methodologically appropriate to mix together mutually exclusive health technology programmes to produce a single ICER representing the cost effectiveness of lapatinib in comparison with 'usual practice'. The blended comparator obscures the result that lapatinib is not a cost effective alternative to capecitabine and vinorelbine and that displacing these technologies with lapatinib would result in an inefficient use of NHS resources. It does not therefore form an appropriate basis for decision making. See FAD section 4.14.

Consultee	Comment	Response
GSK	We would also like to point out that the recommendations of the Committee do not appear to have taken account of the acknowledgement in the methods guides that consideration of the cost effectiveness of a technology should not be the sole basis for decision-making.[3,4] The Committee's decision appears to be based purely on health economic grounds, some of which we believe are not relevant in the current decision making context.	The Committee has considered the importance of patient choice and the oral administration of lapatinib as well as the factors that provide guidance in the NICE guide to the methods of technology appraisal for consideration of ICERs between and above £20-30,000. 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.
GSK	**4. Are there any equality related issues that need special consideration that are not covered in the ACD?** In GSK's original submission, we presented an argument that lapatinib plus capecitabine presents a cost effective alternative to trastuzumab-containing regimens in the subset of patients that is more likely to receive such treatment. This subgroup included patients with progression at an isolated site, patients with few metastases in the soft tissues or bone and patients who experience a previous good response to trastuzumab. However, acknowledging the equity issues associated with trying to identify such a sub-group, and in a sincere attempt to provide equitable access to lapatinib for all eligible patients, GSK offered a patient access programme (LPAP) which demonstrated cost effectiveness of £16,384/QALY, which: - accounts for the key uncertainties in our original analysis, as highlighted by the Evidence Review Group; - includes more recent and robust evidence of the effectiveness of both lapatinib and trastuzumab regimens; - accounts for the current variability in trastuzumab use beyond progression in England and Wales by using an average 'standard practice' comparator.	In the GSK response to the ACD as well as identifying possible subgroups it also acknowledges the difficulty in creating clear and unambiguous clinical criteria with which to define such a subgroup. The Committee considered whether there were any subgroups of patients for whom treatment with lapatinib would be cost effective, such as patients with brain metastases and concluded that trials to establish the effectiveness of lapatinib in subgroups of patients, that included all appropriate treatment comparisons, should be considered. See FAD section 4.17

Consultee	Comment	Response
GSK	The decision not to recommend lapatinib for use on the NHS under the terms of the proposed programme raises several issues concerning the equitable access to treatment in England and Wales: a. There is a clear signal from the clinical community that the unlicensed use of trastuzumab beyond progression will continue to increase in light of the results of the GBG-26 study. Rejecting lapatinib under the terms of the proposed access programme on the basis that its cost effectiveness is dependent on the inclusion of a comparator that is itself cost-ineffective, will be a *de facto* endorsement of the continued cost-ineffective and inequitable use of trastuzumab in this setting, thereby perpetuating the current inequity associated with treatment of these patients, and contributing to the decline in cancer outcomes in England and Wales; b. The guidance for imatinib in chronic myeloid leukaemia[5] suggests that this approach is inconsistent with a decision in similar circumstances (i.e. regarding a cost ineffective comparator), which ultimately will lead to inequality between different populations;	The Committee is unable to make recommendations about comparators in an appraisal. The Committee did not consider that it was methodologically appropriate to mix together mutually exclusive health technology programmes to produce a single ICER representing the cost effectiveness of lapatinib in comparison with 'usual practice'. The blended comparator obscures the result that lapatinib is not a cost effective alternative to capecitabine and vinorelbine and that displacing these technologies with lapatinib would result in an inefficient use of NHS resources. It does not therefore form an appropriate basis for decision making. See FAD section 4.14. The Committee considered the analyses completed against the individual comparators. The Committee was persuaded that the trastuzumab analyses should be considered, but it was not persuaded that they formed an appropriate basis for deciding the cost effectiveness of lapatinib, because the data provided by GSK demonstrated that trastuzumab was in itself not cost effective in comparison with capecitabine. It is accepted that lapatinib is not cost effective in comparison with capecitabine and vinorelbine monotherapies. See FAD section 4.2, 4.3, 4.12, 4.13.

Consultee	Comment	Response
GSK	c. As metastatic breast cancer is incurable, effective treatment options that can delay progression or improve the likelihood of survival without negatively impacting quality of life and adding to the toxicity burden are greatly needed in this patient group. In particular, given that ErbB2-targeted therapy is a crucial component of treatment for patients with ErbB2 positive disease, there is a clear need for alternative ErbB2-targeted therapies. Lapatinib plus capecitabine is a treatment option that has been specifically evaluated and licensed for use when disease has progressed after trastuzumab treatment in the metastatic setting. It is increasingly apparent that proving cost effectiveness of new interventions in late-stage cancer is difficult within the NICE reference case. The background costs of managing these patients is significant and the cost effectiveness estimates are impacted by costs associated with the prolonged survival results in lapatinib patients: even if the lapatinib is provided at zero cost the cost utility ratio in comparison to capecitabine alone is still £11,000/QALY. This means that within NICE's current threshold there is very little spare capacity to justify cost effectiveness, and this may disadvantage patients whose management is, by definition, difficult and expensive.	The Committee considered the wider benefits that may be associated with lapatinib including the provision of a choice of technologies for the treatment of metastatic breast cancer. 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	For these relatively young women the additional time without disease progression afforded by lapatinib can be disproportionately valuable. Whilst the average increase in survival may be limited to months, data from the Lapatinib Extended Access Programme (LEAP, protocol EGF103659)[7] suggest that the benefit to individual patients can be greater than this. The LEAP study, in which patients received lapatinib plus capecitabine according to the licensed indication, and follow-up is still ongoing, found that while the median duration of treatment to date is 24 weeks, the maximum duration to date has been 104 weeks, indicating that some patients are gaining an additional two years of life without their disease progressing. The value of this additional time without progression at this stage of a person's life is not fully represented in the cost/QALY estimates, and clearly does not include any impact on their value to others such as dependents. Recent research would also suggest that the UK public would apply greater priority to diseases with greater severity and hence that in these patients a higher threshold or 'QALY weighting' should be considered.[8]	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.

Consultee	Comment	Response
GSK	d. The draft clinical guideline under consultation[6] highlights a group of patients where the strategy of continuation of ErbB2 suppression with either trastuzumab or lapatinb would be the rational treatment approach (those with progression only in the brain). This reflects what the majority of clinicians would currently do in routine clinical practice; additional local therapies would then be employed to treat the intra-cranial disease. Lapatinib has demonstrated activity in treating established brain metastates[9,10,11] hence there is a strong rationale to consider use of lapatinib in this group of patients with solely intra-cranial disease progression where continued ErbB2 suppression, including trastuzumab, is the standard of care. The current ACD, in rejecting trastuzumab as a comparator on the basis of its cost-ineffectiveness, therefore denies the consideration of lapatinib in the treatment of this important patient group. e. Principle 11 of NICE's Social Value Judgments (NICE 2005)[12] states that whilst not promoting the use of interventions that are clinically and/or cost-effective, it is recognised that individual choice is important for the NHS and its users. As an all-oral combination lapatinib plus capecitabine may be preferred over IV therapy by patients because of quality of life benefits. Wider societal benefits may be possible through the effects on carers of reduced burden of hospital attendance and/or time required for medication administration. We believe that the ACD recommendations do not reflect the spirit of these social values.	The Committee considered that it was appropriate to be mindful of the recommendations from the NICE clinical guideline 81 on advanced breast cancer. The clinical guideline 81 recommends that treatment with trastuzumab should be discontinued at the time of disease progression outside the central nervous system. Treatment with trastuzumab is recommended to be continued only if disease progression is solely within the central nervous system suggesting that trastuzumab is continuing to control disease in the rest of the body. The Committee considered whether it was appropriate to recommend lapatinib for those people who had brain metastases, but was mindful of requests from regulatory agencies for the collection of further trial data to demonstrate this effect. See FAD section 4.17. The 2008 social value judgements indicates that while individual NHS users will expect to receive treatments to which their condition will respond, this should not impose a requirement on NICE's advisory bodies to recommend interventions that are not effective, or are not cost effective enough to provide the best value to users of the NHS as a whole. (Social value judgement principle 5). The Committee considered the wider benefits that may be associated with lapatinib including the provision of a choice of technologies. 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 4.18 to 4.20.

Consultee	Comment	Response
GSK	In conclusion, we believe that the decision to reject lapatinib in combination with capecitabine, in the context of the Lapatinib Patient Access Programme, means that patients for whom there are few options available will be denied access to a proven treatment which is licensed, cost effective overall, and cost saving when compared with the intervention most commonly used in clinical practice. If current practice continues, this will inevitably lead to further inequality in access to medicines for these patients across England and Wales. ***References provided but not reproduced here*** ***Response to DSU report included but not reproduced***	See responses above.

Consultee	Comment	Response
NCRI Breast CSG, RCP, RCR, ACP, JCCO	We have reviewed the draft recommendations announced by NICE in the second technology appraisal consultation document (ACD) that suggests that lapatinib (Tyverb) should not be used in the NHS, except within the context of clinical trials. This recommendation seems to be based on an economic argument that continues to disregard the reality of the current clinical situation in the UK where trastuzumab is frequently given beyond progression with capecitabine or other cytotoxic regimens. To illustrate the extent of unlicensed use of trastuzumab beyond progression the NCRI Breast Cancer Study Group conducted an e-mail poll of UK oncologists. Oncologists were asked whether they used trastuzumab beyond progression, and if they did, to provide both an estimate of the proportion of patients seen and the absolute numbers per year in their care who receive trastuzumab for progressive systemic disease, other than those with brain metastases where the use beyond progression is less contentious (Appendix 1). Due to time constraints only a four-day response time was allowed, but this generated replies from 81 clinical and medical oncologists with special expertise in the management of advanced breast cancer. These replies came from 28 English and 3 Welsh service networks as well as, 2 Scottish networks and 1 from Northern Ireland. Of 81 respondents 33 admitted to use of trastuzumab in >75% of their patients, 20 in 50-74%, 8 in 25-49%, 12 in 1-24% and only 8 either never used trastuzumab beyond progression or had no clinical experience of this particular clinical situation. Minimum estimates of numbers of patients receiving trastuzumab beyond progression totaled 745 patients per year. Bearing in mind that not all oncologists involved in the treatment of advanced breast cancer responded and that around 20% of patients progress first in brain and will also receive trastuzumab beyond progression, it is clear that considerably more than 50% of patients in the country are receiving this treatment (Appendix 2).	The Committee has specifically considered the use of trastuzumab after progression of disease. It was persuaded by the evidence submitted included that from yourselves 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
NCRI Breast CSG, RCP, RCR, ACP, JCCO	In recognition that the first ACD from NICE did not consider lapatinib to be cost effective in treating this patient population, Glaxo Smith Kline (GSK) proposed an innovative patient access programme, where the company would bear the cost of lapatinib for all eligible patients, for up to the first 12 weeks of treatment. The NHS would commence payment only for the patients who continue to receive clinical benefit beyond 12 weeks. This programme was designed to provide access to all eligible patients and deliver cost- effectiveness at a threshold that should have been acceptable to NICE. We consider that this is a very responsible acknowledgement of the cost pressures of incorporating another expensive drug into routine NHS practice and tips the economic argument firmly in favour of lapatinib in place of the current standard of care. In our view the use of lapatinib plus capecitabine will ultimately reduce the costs to the UK health system compared to the established but unlicensed clinical practice of continuing to use trastuzumab once a patient's disease has progressed. The relevant merits of lapatinib or trastuzumab beyond progression are clearly an important research question that the UK oncology community would be happy to address in a well-designed randomised clinical trial.	The Committee considered the patient access programme and did not consider that application of the patient access programme to the blended comparator was appropriate because of the limitations of using a blended comparator. See FAD sections 4.10, 4.14 and 4.15.
NCRI Breast CSG, RCP, RCR, ACP, JCCO	Appendix 1: Questionnaire to breast oncologists – October 2008. ***(included but not reproduced here)***	Noted, this evidence has been considered by the Committee. See FAD sections 4.2 and 4.3.
NCRI Breast CSG, RCP, RCR, ACP, JCCO	Appendix 2: Anonymised results from questionnaire ***(included but not reproduced here)***	Noted, this evidence has been considered by the Committee. See FAD sections 4.2 and 4.3.

Consultee	Comment	Response
Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care and Macmillan Cancer Support.	Thank you for the opportunity to comment on the consultation document for the appraisal of lapatinib for breast cancer. We have reviewed the evidence that was presented in the second ACD, including the additional data which has been provided by the manufacturer. Following this, we have jointly concluded that we have no additional comments to make further to our collaborative response submitted on 28th July 2008 from Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care and Macmillan Cancer Support. We would, however, like to take this opportunity to reiterate that 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 tumors overexpress HER2. As patient organisations, we would like to emphasise how important it is to offer patients greater treatment choice, especially for patients with metastatic disease who often have limited treatment options. We acknowledge the limitations in the data at the present time including the concerns over the remaining uncertainties and we welcome the call for further research to identify appropriate sub-groups to receive lapatinib treatment (such as patients with brain metastases).	The Committee considered the wider benefits that may be associated with lapatinib including the provision of a choice of technologies for the treatment of metastatic breast cancer and was not persuaded that the importance of patient choice should alter their decision about lapatinib being an appropriate use of NHS resources. 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 4.16. 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 4.18 to 4.20.
Royal College of Nursing	The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) of the technology appraisal of Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer. Nurses working in this area of health have reviewed this document and have no further comments to add. The RCN would welcome guidance to the NHS on the use of this health technology.	Comments noted, no actions required

Consultee	Comment	Response
Patient expert 1	Thank you for the opportunity to comment as a patient expert on the consultation document for the appraisal of lapatinib for breast cancer. I have nothing further to add to the comments I gave at the committee meeting. I would also like to reiterate that I support the comments given in the joint submission sent in July from Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care and Macmillan Cancer Support and the letter submitted by these organisations in October.	Comment noted, see responses to the joint submission from Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care and Macmillan Cancer Support.

Consultee	Comment	Response
Clinical specialist 1	Thank you for your e mail. Yes I consider that all the relevant facts have been taken into account. My over-riding concern is that lapatinib does not have an overall survival advantage, something one would hope for in 'last line' therapy. In earlier therapy survival is harder to obtain, due to subsequent cross over but in later therapy it should be sought after and ideally a significant difference found (I am attaching an editorial I wrote this month addressing this issue). Having said this, it is an oral tablet, for use in a very specific population, and one in whom there are no other therapeutic options for. It is safe and well tolerated and the toxicities appear related to the concurrent capecitabine that is taken with it. It is difficult to say with any certainty, due to lack of robust evidence, whether re-treatment with Herceptin should represent a comparator arm in cost-effectiveness analyses at least. Overall, 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 and covered by the documents. The provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. Thank you in advance for asking my opinion. I would be delighted to help out in future projects. ***Editorial included but not reproduced***	Comments noted, no actions required.

Comments received from commentators

Commentator	Comment	Response
National Collaborating Centre for Cancer	"The GDG regrets that even under the terms of the access scheme proposed by GSK lapatinib proves not to be cost effective. The GDG supports the draft recommendations. The GDG would be most concerned if the Appraisal Committee were to accept the use of trastuzumab on disease progression as a comparator, as to do so would be implicitly to endorse that application of this high cost intervention without first performing a cost effectiveness analysis. To do so would also run counter to the recommendations made by the GDG in this area. Evidence of clinical effectiveness of the second line use of trastuzumab in combination with chemotherapy in the various reports by von Minckwitz et al became available only towards the end of the guideline preparation process, so that any cost effectiveness analysis was not possible. The GDG strongly believes such an evaluation should be performed urgently, and would support subsequent evaluation in the STA process. We do not think that such an expensive treatment strategy should be undertaken in the NHS without such an evaluation."	Comments noted, no actions required.

Commentator	Comment	Response
Roche Products	**1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT** **a) The ACD does not provide the latest hazard ratio (HR) for time to progression (TTP) of 0.72 (Lapatinib SmPC, June 2008) from the registration trial of lapatinib in combination with capecitabine versus capecitabine monotherapy. (section 3.20)** Section 3.3 of the ACD states that: "***The results reported here all relate to the analysis done using data for the April 2006 cut-off date unless otherwise stated***" The original planned interim analysis of the pivotal lapatinib trial EGF100151 took place after a data lock on 15th November 2005. The interim analysis, after 114 disease progression events, demonstrated a 4 month improvement in median TTP (4.4 months with C vs 8.4 months with LC, HR 0.49; P<0.001; Geyer et al NEJM 2006). An updated analysis which included all 399 patients who entered the trial to April 2006 was presented by Prof. Cameron during the ASCO 2007 meeting (Abstract 1035) and subsequently published in *Breast Cancer Res Treat* in January 2008 (submitted and accepted 21 December 2007). This analysis which took place after 184 TTP events, showed the absolute benefit in median TTP had changed from 4 months to 2 months (4.3 (C) to 6.2 (LC) months, HR 0.57; P<0.001; Cameron et al *Breast Cancer Res Treat* 2008)	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 0.72 and 0.57 respectively). A time to progression hazard ratio of 0.49 was not used in the analyses. See the GSK response to the report produced by the DSU.

Commentator	Comment	Response
Roche Products	This updated analysis of the pivotal lapatinib trial, EGF100151, has been in the public domain since presentation at ASCO, June 2007 and appears to have been omitted from the previous submissions made by the manufacturer (original submission [17 April 2007] and from the response to the first ACD [28 July 2008]) and is therefore not included in the current economic model submitted as an addendum. The updated economic analysis of lapatinib includes the latest TTP and OS data for the trial of trastuzumab and capecitabine (GBG-26) which was first reported at ASCO in June 2008. Updated assumptions about trastuzumab administration based on data from the GBG-26 study were also included in the lapatinib ACD. In summary, there appears to be a mixture of old and new data contained within the updated economic model and therefore we provide the latest available data reported from analyses of the pivotal lapatinib trial EGF100151 and the trastuzumab study GBG-26 in Table 1 below. **Table 1: Comparison of hazard ratios and incremental benefit in TTP based on GBG-26 and EGF100151 studies**. ***(included but not reproduced here)***	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 0.72 and 0.57 respectively). A time to progression hazard ratio of 0.49 was not used in the analyses. See the GSK response to the report produced by the DSU.

Commentator	Comment	Response
Roche Products	**Decrease in hazard ratio of the overall survival results published in the lapatinib SmPC** In section 3.12 of the ACD, the updated LC overall survival data (lapatinib SmPC June 2008) are discussed and the message conveyed is that the OS results have improved in the latest cut-off of the data. Although this is correct in terms of the absolute improvement in weeks, these results show that the updated incremental benefit (HR=0.9; 95% CI 0.71, 1.12) for the LC arm has also decreased since the previous analysis. **c) Previous comments in Roche's response to the first ACD regarding the comparison of hazard ratios from GBG-26 and EGF 100151 have not been taken into consideration in the second ACD** In the round of consultation on the first ACD, Roche also drew to the Appraisal Committee's attention that a more recent analysis of the data for time-to-progression (TTP) from the lapatinib registration trial had been published (Cameron et al 2008). This new information was not included in the revised base-case economic model and was therefore not used in the ERG's and the DSU's analyses. The September 2007 follow-up illustrates that the treatment effect of LC compared to capecitabine monotherapy is not as large as that demonstrated by the 2006 follow-up data utilised in the cost-effectiveness calculations for TTP (see Table 1). This is an extremely important considering the large effect this has on the ICER and therefore so should be taken into account by the Appraisal Committee.	The text in FAD section 3.4 has been amended to reflect this more clearly. See FAD section 3.4. The revised economic analyses included updated survival data (hazard ratio 0.90). The manufacturer of lapatinib confirmed that there is no September 2007 time to progression data. No changes made to the FAD.

Commentator	Comment	Response
Roche Products	**Trastuzumab administration frequency and dosing appear to be incorrect** Since the last ACD consultation, the licence of trastuzumab has been amended to include both weekly and three weekly administration for patients with metastatic breast cancer. The SmPC has been changed accordingly and the September 2008 version states the following: "**MBC 3-weekly schedule:** Initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes." The licence now reflects clinical practice. Two market research studies commissioned by Roche indicate that trastuzumab is now overwhelmingly given as a 3-weekly regimen in the treatment of MBC. <u>Double Helix Development study</u> DHD is an independent market research agency and was commissioned to conduct a market research study which was fielded in May - June 2008. One of the objectives of the study was to assess whether trastuzumab is given as either a weekly or a 3-weekly regimen in EBC and MBC. In order to meet Roche's research objectives, Double Helix Development designed a Patient Case Record (PCR) approach. A sample of oncologists (n=85) completed PCR forms for the last three HER2-positive MBC patients seen who were currently receiving anti-cancer drug treatment for MBC. The breakdown of the respondent sample can be found in Appendix 1.	The Committee discussed the frequency of trastuzumab administration and noted that 3 weekly administration was likely to reflect clinical practice. See FAD section 4.12.

Commentator	Comment	Response
Roche Products	Of the respondents, 70% were Consultants and 30% were Specialist Registrars. All had been practising for between 4 and 30 years and were responsible for treatment decisions for HER2-positive breast cancer patients. The sample was spread across UK cancer networks. The breakdown of the cancer networks included in this research can be found in Appendix 1. The main outcome of the study was that trastuzumab is given as a 3-weekly regimen in 96% of patients. <u>Genactis study</u> This market research was conducted in Q4 2007 by Genactis and its main objective was to gain an in-depth understanding of the MBC market and treatment patterns. The study is descriptive market research using a multiple cross-sectional design. Data collection was achieved by sending Electronic Case Assessment Forms (eCAFs) to physicians. Physicians of 15 prospective patient cases of MBC, commencing a line of treatment, were asked to complete an eCAF and return it to Genactis for analysis. Although this was multicentre and multinational study, the UK was represented by 74 respondents who completed 1110 forms. A total of 1064 forms were collected and analysed. 207 eCAFs included treatment with trastuzumab in the MBC setting. Out of all the 207 patients treated with trastuzumab only 8% were given the weekly regimen, 92% of the patients received the 3-weekly treatment regimen. Both market research studies demonstrate that trastuzumab is given as a 3-weekly regimen in 92% to 96% of all MBC patients treated. Although the base-case scenario in the cost-effectiveness analysis has been revised, it still does not reflect treatment patterns observed in UK as demonstrated by the above data.	The Committee discussed the frequency of trastuzumab administration and noted that 3 weekly administration was likely to reflect clinical practice. See FAD section 4.12.

Commentator	Comment	Response
Roche Products	**2 WHETHER 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** **a) Key elements of the patient access programme are unclear and there is insufficient detail to enable an accurate assessment of clinical effectiveness (sections 3.17, 4.14)** Having reviewed the information on the '*Patient Access Programme*' proposed by GSK, Roche believes that the scheme lacks to a certain degree the transparency required to undertake a thorough evaluation. The main concerns are focussed around the timing of assessments and continuation/discontinuation criteria and how these affect the cost-effectiveness of the scheme. Although the manufacturer states, "clear criteria will be defined for entry into the programme, as well as continuation and stopping criteria" these are presently unclear in the ACD and therefore Roche believes that further details are required. **Continuation/discontinuation criteria** Roche is concerned that the criteria are very subjective and not as rigid as they could be which may result in subjective decision making and hence regional differences in treatment practice. Currently the continuation criteria are clinical benefit characterised by the reduction in size or disappearance of existing lesion (whether measurable or not), stable disease and/or improvement of other response criteria including symptom improvement. This may mean that patients could continue treatment because of perceived symptomatic benefit even though in some case this may be a placebo effect.	Comments noted. The Committee considered the lapatinib patient access programme. See FAD sections 4.10 and 4.15.

Commentator	Comment	Response
Roche Products	The criteria may result in inappropriate treatment of patients on lapatinib and capecitabine. An accurate assessment of patients and stringent criteria for stopping or continuing treatment will determine the treatment duration which influences the cost of lapatinib to the NHS, particularly if more patients than expected continue treatment on lapatinib and capecitabine.	Comments noted. The Committee considered the lapatinib patient access programme. See FAD sections 4.10 and 4.15.
Roche Products	**Economic evaluation critique** The scheme itself and how it integrates with the manufacturer's base-case cost-effectiveness analysis has been inadequately presented for consultation. The main characteristic of the scheme is that a certain percentage of the eligible population will drop-out by the 12th week of treatment. It is unclear if this drop-out/discontinuation rate is the same as the one used in the base-case analysis. If the rate has been assumed to be greater in the scheme than in the base-case model, it would have a direct impact on the cost-effectiveness of the lapatinib treatment as more patients are assumed to stop treatment in the scheme than observed in the trial. The scheme seems to preserve the QALYs gained from the trial data while more patients are assumed to drop-out based on the clinical criteria. Finally, we also note that the NHS has to initially pay for the treatment for the first 12 weeks that are part of this scheme and that they have to claim back the costs from the manufacturer. As is evident from the manufacturer's submission it is possible that the claim for reimbursement of costs may be refused if they deem that inclusion criteria have not been met and therefore may result in a unexpected cost to the NHS.	Comments noted. The Committee considered the lapatinib patient access programme. See FAD sections 4.10 and 4.15.

Commentator	Comment	Response
Roche Products	**b) The ACD does not provide an accurate summary and representation regarding the clinical significance of trastuzumab beyond progression (section 4.4)** The Appraisal Committee questioned the clinical significance of continuing trastuzumab beyond progression in patients with metastatic disease. Roche would like to draw the Committee's attention to a randomised clinical trial, GBG-26 (von Minckwitz ASCO 2008) and a single arm prospective trial (Bartsch JCO 2007) which all provide consistent results demonstrating that continuation of trastuzumab beyond progression (in combination with chemotherapy) extends survival compared with stopping trastuzumab on progression. The comment made by the DSU in the ACD that the HR for TTP derived from the GBG-26 trial was associated with methodological limitations because randomisation was not maintained is inaccurate; randomisation was maintained, however, the trial was closed early on the recommendation of the Independent Data Monitoring Committee (IDMC).	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. The comment made by DSU did not refer to trial HR but referred to the digitalised HR produced by the manufacturer of lapatinib when an indirect comparison of trials EGF100151 and GBG-26 was completed.

Commentator	Comment	Response
Roche Products	**GBG-26 Study design** The GBG-26 study is a randomised phase III trial, endorsed by the Breast International Group (BIG 3-05; Appendix 2). The results were presented by von Minckwitz et al at ASCO 2008 (Abstract 1025). Patients who 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 capecitabine (TC) or stop trastuzumab treatment and receive capecitabine monotherapy (C). The trial planned to recruit 241 patients per arm but closed early on the advice of the IDMC in May 2007, after recruitment of 78 patients per arm. There were two main reasons: • FDA registration of lapatinib plus capecitabine for trastuzumab progressors. Although GBG-26 was a European study it was believed the EU license for lapatinib in this setting would be granted imminently • Slow accrual due to unwillingness of HER2-positive patients to stop trastuzumab and therefore enter the capecitabine monotherapy arm.	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.
Roche Products	**Results of GBG-26 demonstrated a statistically significant 3 month improvement in TTP for continuing trastuzumab beyond progression versus stopping treatment** The study was originally designed with 80% power to detect a 27.5% improvement in TTP from 4 to 5.1 months for continuing trastuzumab beyond progression. The trial recruited 78 patients per arm and those who continued trastuzumab beyond progression demonstrated a 46% improvement in median TTP from 5.6 (C) to 8.2 (TC) 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) versus patients who stopped trastuzumab on progression. It emerged during the analysis of GBG-26, that the advantage of continuing trastuzumab beyond progression exceeded the predicted magnitude of benefit such that the number of patients recruited clearly demonstrated a statistically significant and clinically relevant advantage when trastuzumab was continued beyond progression.	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.

Comments received from members of the public

Role*	Comment	Response
Web comment 1	depriving a minority group of patients the only effective option available Widely avialable US and Europe and ongoing big neo and adjuvant trials Relatively small nos involved Toxicity in practice not major feature Thus can provide good palliation Qaly ideal for chronic conditions -diabetics -but not for metastatic cance Decision has resulted in post code lottery prescribing becoming an issue sadly	The Committee considered the wider benefits that may be associated with lapatinib including the provision of a choice of technologies for the treatment of metastatic breast cancer and was not persuaded that 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.

* 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.

Role*	Comment	Response
Web comment 2	On a molecular basis the manufacturer does not demonstrate any difference from existing drugs. There is no statement with regard to the expiry of patents. Having read the evidence as presented on line I feel that there is a substantial lack of disclosure by the manufacturer in respect of 1) who conducted the trials and what if any associations do they have with the manufacturer even if arms length 2) where were they conducted and under what criteria 3) disclousre of all results 4) a lack of comparison of like with like including older drugs which maybe just as efficacious 5) the complete disregard for alternative methods and prevention. Identification of clinical specialists would be appropriate and verification of no financial or other links with the manufacturer. The committee should make it clear that any such trials must be totally independent in every form from the manufacturer and all data available for consideration. Consideration should also be given to including other forms of treatment and comparison.	Comments noted. The manufacturer of lapatinib has submitted information in accordance with the template provided by NICE. The comparators used in the appraisal include all those identified in the scoping document which sets the boundaries within which guidance is produced. No changes to the FAD required.

Role*	Comment	Response
Pharmaceuticals manufacturer	**Comments regarding the ACD** [redacted] believe that all the relevant evidence has been taken into account although, as described by the Appraisal Committee within the ACD, the manufacturer's submission is dependent on accepting the validity of key assumptions that are not supported with robust trial based evidence. As stated in the ACD there is a need for credible research to support the following:- • dosing regime • combination therapies • clinical subgroups of patients likely to benefit. Without robust data to better quantify these variables in the economic analysis, it is unlikely that cost-effectiveness can be determined with the degree of certainty that the Appraisal Committee require to ensure that lapatinib constitutes a good use of NHS resources. [redacted] believes that without evidence of clinical equivalence in efficacy vs. Herceptin in this or any other breast cancer patient group, clinical effectiveness cannot be shown. This rational extends to sub-groups such as these patients with brain metastases. This makes any subsequent cost effectiveness arguments inconsequential. Regarding the summary of cost effectiveness, [redacted] believe that some aspects may be worth further consideration by the Appraisal Committee specifically, it would be helpful to explore the market research on wastage of Herceptin as this has a significant influence on the cost effectiveness of lapatinib. The degree of uncertainty around this estimate is likely to be an important consideration for the Committee.	Comments noted, no changes to the FAD required. The Committee considered in detail the assumptions in the model about the wastage of trastuzumab. See FAD section 4.12.

Role*	Comment	Response
Pharmaceuticals manufacturer	In **Section 3.6,** the ACD states that the economic model did not explicitly include the impact of treatment-related adverse events on quality of life. The rationale for this omission is unclear since the impact of adverse events on quality of life is an important consideration in establishing the cost - benefit of lapatinib. Further more, the impact of adverse events is a fundamental decision driver for prescribers and patients when evaluating the merits of different treatment options. We fully recognise the importance of considering equality related issues within the context of this appraisal. There are specific subgroups of patients that could benefit from access to lapatinib (i.e. the progression of disease during treatment with Herceptin or metastasis to the brain with or without Herceptin); however, we would strongly suggest that more substantial research is required before specific recommendations are made for these patient groups. The Appraisal Committee has clearly undertaken a pragmatic approach to this evaluation and made a recommendation that reflects both the paucity of data and uncertainty surrounding the key assumptions. The issues raised in our response are unlikely to change the Committee's overall recommendation.	Comments noted. The Committee considered the importance of adverse events. See FAD section 4.6, 4.7. Comments noted, no change to the FAD required.

Organisations stating that they had no comments:

Department of Health

Summary of comments received from members of the public

Theme	Response
No responses received	N/A