NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Lapatinib for metastatic breast cancer

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD 3)

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
Glaxo SmithKline (GSK)	Thank you for the opportunity to respond to the Appraisal Consultation Document for lapatinib (October 2009). GlaxoSmithKline is extremely disappointed that the draft guidance does not recommend lapatinib for use in the NHS, despite consideration under the supplementary advice to Appraisal Committees on appraising end of life medicines (EoL guidance). The EoL guidance was specifically developed to help small numbers of patients, who have limited time to live, gain access to important new medicines. The additional data submitted by GSK in response to points upheld at the appeal in June 2009 demonstrated that lapatinib met all three of the criteria for consideration under the EoL guidance but the Appraisal Committee concluded that lapatinib is still not a cost-effective use of NHS resources despite GSK offering the Tyverb Patient Access Programme (TPAP), which allows NHS patients in the UK free access to lapatinib for the first three months of treatment. Our comments on specific aspects of the ACD are structured below under the questions requested by NICE.	Comments noted. See responses below.
GSK	**Do you consider that all of the relevant evidence has been taken into account?** GlaxoSmithKline considers that the ACD does take into account the relevant evidence.	Comment noted. No actions required.

Consultee	Comment	Response
GSK	**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 welcome the Appraisal Committee's acknowledgement that the evidence presented by GSK suggests that treatment with lapatinib plus capecitabine may increase survival by around 3 months compared with capecitabine alone. However, the Committee expresses concern about the robustness of the overall survival estimates, in particular the adjustments made to take account of patients crossing from the capecitabine arm to the lapatinib combination arm following the early termination of study EGF100151. Whilst we agree that alternative methods of minimizing the impact of crossover effects might indeed be employed, we would argue that any statistical method will have inherent deficiencies. The Decision Support Unit's preference for the methods of Robins and Tsiatis (1991) and Branson and Whitehead (2002) is based on a study funded by NICE, which is unpublished and was therefore unavailable to GSK at the time of submission.	Comment noted. The Committee heard from the DSU that it considered that the methods used to adjust for crossover may have led to some bias in the estimates and that there were alternative methods that might be more valid and might give different estimates. The Committee was not therefore persuaded that the adjusted estimates of overall survival presented by the manufacturer led to estimates which were any more valid than the unadjusted estimate of 2.4 months. However, the Committee noted that there was a minor chance that lapatinib plus capecitabine might offer an increase in overall survival of 3 months compared with capecitabine alone. It therefore concluded that it should consider the ICERs in light of the end-of-life considerations. See FAD section 4.21
GSK	Several alternative approaches were explored and presented in GSK's submission of 25 August 2009. It should be noted that these were not bespoke analyses initiated for the purposes of the NICE post-appeal submission; rather, they were performed primarily to support the regulatory process for lapatinib which was ongoing in parallel. The method chosen by GSK as most representing the likely effects of lapatinib on overall survival for both regulatory and NICE purposes (Cox regression model considering cross-over as a time dependent covariate) was selected as it addresses some specific issues associated with this type of dataset. The time dependent analysis models each patient in one of two states over time: the first state represents the arm to which the patient was randomized; the second state represents cross-over to lapatinib + capecitabine. This model reflects the time at which the patient changes from capecitabine treatment to	Comment noted. The Committee considered all the analyses provided by GSK. The Committee heard from the DSU that it considered that the methods used to adjust for crossover may have led to some bias in the estimates and that there were alternative methods that might be more valid and might give different estimates. The Committee was not therefore persuaded that the adjusted estimates of overall survival presented by the manufacturer led to estimates which were any more valid than the unadjusted estimate of 2.4 months. However, the Committee noted that there was a minor chance that lapatinib plus

Consultee	Comment	Response
	treatment with the lapatinib/capecitabine combination. The hazard up to the time point of cross-over for patients in capecitabine group is due to monotherapy capecitabine. The hazard from the time the patient crosses over to lapatinib/capecitabine is due to the combination therapy. GSK believes that this method is appropriate since it accounts for the effects of capecitabine up to the point of cross-over, as well as for the effects of the lapatinib/capecitabine combination from that point for those patients who have crossed over.	capecitabine might offer an increase in overall survival of 3 months compared with capecitabine alone. It therefore concluded that it should consider the ICERs in light of the end-of-life considerations. See FAD section 4.21.
GSK	Interestingly, the Decision Support Unit (DSU) reports that excluding switching patients from the analysis altogether gives relatively small biases in situations with a low proportion of switchers, but they do not give any indication of what is considered a low proportion. The number of patients who crossed over to the combination arm was 36 (out of 201 patients in the capecitabine arm (18%); around 9% of the study total), which we would argue is a relatively low proportion. The analysis which excluded these patients altogether yielded a median overall survival estimate of 4.3 months, which is well above the end of life criterion threshold of 3 months. The DSU also comments that the method of Branson & Whitehead is particularly robust in settings when a high proportion patients switched, which we believe is not the case in study EGF100151. To summarise we support the Committee's conclusion that lapatinib combination treatment may improve survival by 3 months or more compared with capecitabine monotherapy, but believe that their interpretation of the estimates as lacking robustness should be reconsidered in the context of the above arguments.	Comment noted. See responses above.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td>GSK</td><td>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?

GSK does not consider that the provisional recommendations in the ACD constitute a suitable basis for guidance to the NHS.
Having concluded that the evidence presented by GSK suggests that treatment with lapatinib plus capecitabine may increase survival by around 3 months compared with capecitabine alone, the Appraisal Committee considered the cost effectiveness results for lapatinib in combination with capecitabine under the EoL guidance (results shown in Table 1 overleaf).</td><td>Comments noted. See responses below.</td></tr>
<tr><td>GSK</td><td>The Committee did not consider that the impact of increasing QALY weighting such that the increased survival is experienced at the quality of life expected of a healthy individual (effectively reducing the ICER from £59,441/QALY to £45,525/QALY) was acceptable.

Furthermore, the magnitude of additional weight (a factor of around 2) that would need to be assigned to the QALY benefits for the base-case ICER of £59,441/QALY to fall within the current threshold range was deemed by the Committee to be unacceptable, with the conclusion that lapatinib would not be a cost-effective use of NHS resources.

Table 1. Cost effectiveness results for lapatinib in combination with capecitabine versus capecitabine considered in the context of end of life guidance
<table><tr><td>Analysis</td><td>ICER £/QALY</td></tr><tr><td>Cost effectiveness including patient access scheme</td><td>£59,441</td></tr><tr><td>As above and assuming additional life years gained experienced at same utility (0.85) as healthy individual</td><td>£45,524</td></tr></table></td><td>The Committee considered the cost-effectiveness analyses provided by the manufacturer under the supplementary advice on end of life. The Committee considered that the magnitude of additional weight that would need to be assigned to the QALY benefits for the base-case ICER of £59,400 per QALY gained to fall within the current threshold range was not acceptable. The Committee further considered that the magnitude of greater weight that would need to be given to the QALYs gained in the later stages of terminal disease, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy person of the same age, was also not acceptable. Therefore, the Committee concluded that lapatinib as a treatment for women with previously treated advanced or metastatic breast cancer would not be a cost-effective use of NHS resources. See FAD section 4.23.</td></tr>
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Consultee	Comment	Response
GSK	We are concerned that NICE's rejection of lapatinib as an option at this level of cost effectiveness fails to account fully for lapatinib's potential benefits and the setting in which it is currently indicated, especially in the context of other appraisals where similar levels of cost effectiveness have been accepted (NICE 2009a). We would also like to highlight a lack of transparency in the ACD regarding the specific reason/s why the estimated level of cost effectiveness of lapatinib in combination with capecitabine is unacceptable when considered under EoL guidance.	The Committee discussed the level of increment of QALY above its usual threshold range that might be acceptable at a potential extension of life of 3 months. It took into account the unique and innovative aspects of lapatinib, patient need, and previous appraisals where judgements were made on the basis of end-of-life supplementary advice. The Committee was also mindful of the uncertainty around the estimates of overall survival gain for lapatinib. Taking these factors into account it considered that the magnitude of additional weight that would need to be assigned to the QALY benefits for the base-case ICER of £59,400 per QALY gained to fall within the current threshold range was not acceptable. See FAD section 4.23.
GSK	The basis of a decision regarding whether lapatinib constitutes an effective use of NHS resources must necessarily take into account a range of factors in addition to an estimate of its cost effectiveness against a single comparator at a fixed cost effectiveness threshold, e.g. the level of unmet medical need, current clinical practice, end of life considerations, degree of innovation, patient choice, route of administration. We welcome NICE and the Appraisal Committee's consideration of some of the wider issues associated with the treatment of this group of women who have few therapeutic options available to them other than continued trastuzumab, through the EoL guidance and ACD/FAD development processes. However, we are concerned that the selected issues have largely been considered in isolation, and might not individually constitute a justification for the approval of lapatinib, whereas if considered collectively they might lead to a different decision that better reflects the realities of the management of these women. GSK believes that there are several important and exceptional factors which should be taken into account collectively in making the decision as to whether the introduction of lapatinib is an appropriate use of NHS resources.	While considering the Institute's supplementary advice on end of life, the Committee also considered the wider benefits that may be associated with lapatinib. However, it was not persuaded that the benefits associated with the mode of administration of lapatinib, innovation or the importance of patient choice should alter its decision about lapatinib being an appropriate use of NHS resources. See FAD section 4.17.

Consultee	Comment	Response
	These are outlined below:	
GSK	*Current management of relapsed HER2 positive breast cancer* Regardless of the probability that trastuzumab continued beyond progression is unlikely to be cost effective and therefore should be eliminated from consideration in an incremental cost effectiveness analysis, the reality is that trastuzumab will continue to be used to a degree in this clinical setting, based on the current body of evidence supporting continued HER2 (ErbB2) suppression as the basis of treatment in this setting. The cost effectiveness analysis underpinning the current appraisal consultation is restricted to a comparison with single agent capecitabine. Even if the use of trastuzumab beyond progression decreases as a result of NICE Clinical Guideline 81 (which recommends that treatment with trastuzumab should not be discontinued if disease progression is only within the central nervous system (CNS), but that it should be discontinued at the time of disease progression outside the CNS) its use is unlikely to be eradicated. The ICER of £59,441/QALY does not take into account any impact on cost effectiveness of the continued use of trastuzumab in this setting, some of which will be legitimate according to the guideline (patients with CNS progression). Nor is the impact of an all-oral regimen (in the context of continued trastuzumab use) captured in this figure. This ICER is therefore an over estimate of the true ICER for lapatinib plus capecitabine compared with routine clinical practice (i.e. lapatinib treatment is likely to be more cost effective than it appears).	Comment noted. 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 routine clinical practice. See FAD sections 4.14 and 4.15. The Committee specifically considered whether lapatinib should be considered as an option for those people for whom the NICE clinical guideline (CG81 'Advanced breast cancer: diagnosis and treatment') recommends continuing trastuzumab after progression, namely those whose disease progresses only in the central nervous system. However, it considered that lapatinib had not been demonstrated to be cost effective in the subgroup of patients with disease progression only in the central nervous system. See FAD sections 4.16 and 4.25.
GSK	*Potential for savings to the NHS* GSK has made lapatinib available via a patient access programme (the TPAP), designed to facilitate equitable patient access to treatment and to maximise value to the NHS by linking payment for lapatinib to clinical benefit. Under the terms of the TPAP the initial cost of lapatinib, up to a maximum of 12 weeks, is borne by GSK. The NHS only funds lapatinib for patients continuing to derive clinical benefit beyond 12 weeks. The potential for any cost savings is especially pertinent in the context of	The Committee was not persuaded that the analyses comparing lapatinib with trastuzumab formed an appropriate basis for deciding the cost effectiveness of lapatinib. See FAD sections 4.13, 4.24-4.26. The Committee specifically considered whether lapatinib should be considered as an option for those people for whom the NICE clinical guideline (CG81 'Advanced breast

Consultee	Comment	Response
	treatment of women whose disease has progressed only in the brain, for whom continued trastuzumab-based therapy is advocated. For patients who would otherwise be treated with trastuzumab at a cost of £1,222 per 3-week cycle (6mg/kg 3-weekly for average weight woman of 59.5Kg), treatment with lapatinib (£1,206.45 per 3-week cycle) is marginally less costly at list price, but this saving is increased substantially under the terms of the TPAP whereby the NHS will pay for lapatinib only after 12 weeks (i.e. 4 cycles). Furthermore, as an orally-administered regimen, lapatinib plus capecitabine would also help to reduce pressure on hospital-administered IV cancer therapy service capacity as well as on pharmacy workload since there is no need for reconstitution prior to administration. It may be of interest to note that to date 27 NHS Trusts have entered into contracts for TPAP, reflecting the clinical demand for lapatinib and recognising its potential value to the NHS.	cancer: diagnosis and treatment') recommends continuing trastuzumab after progression, namely those whose disease progresses only in the central nervous system. However, it considered that lapatinib had not been demonstrated to be cost effective in the subgroup of patients with disease progression only in the central nervous system. See FAD sections 4.16 and 4.25.
GSK	*Management of patients with disease progression in the central nervous system* NICE Clinical Guideline 81 on the diagnosis and treatment of advanced breast cancer recommends that treatment with trastuzumab should not be discontinued if disease progression is only within the central nervous system (CNS), but that it should be discontinued at the time of disease progression outside the CNS. Between 28% and 43% of patients receiving trastuzumab in the metastatic setting have been reported to relapse with brain metastases (Bendell 2003; Lin 2004). The continued use of trastuzumab beyond progression as advocated by the clinical guideline is therefore likely to be significant in the population eligible for lapatinib even if it is restricted to the particular sub-group of patients who have progressed only in the CNS. Lapatinib represents the only licensed alternative to trastuzumab for patients who have progressed in the CNS whilst taking trastuzumab. There is good evidence to suggest that control of non-CNS disease by lapatinib is comparable to that afforded by trastuzumab (Gomez 2008, Vogel 2002). In addition, as lapatinib is a small molecule, it is able to cross the blood-brain-barrier and penetrate the CNS (Van den Abbeele 2006; Gril 2008) and there is evidence that it has activity in both treating (Lin 2008; Lin 2009) and	Comment noted. The Committee specifically considered whether lapatinib should be considered as an option for those people for whom the NICE clinical guideline (CG81 'Advanced breast cancer: diagnosis and treatment') recommends continuing trastuzumab after progression, namely those whose disease progresses only in the central nervous system. However, it considered that lapatinib had not been demonstrated to be cost effective in the subgroup of patients with disease progression only in the central nervous system. See FAD sections 4.16 and 4.25.

Consultee	Comment	Response
	reducing the incidence of brain metastases as a first site of relapse (Cameron 2008). As highlighted in our submission on EoL considerations (25 August 09) in the Lapatinib Expanded Access Programme (LEAP), a sub-population of patients with progressive brain metastases following whole brain radiotherapy and trastuzumab within a UK cohort showed favourable response rates to lapatinib plus capecitabine with times to disease progression identical to the whole cohort. There will be patients who have progressed in the CNS for whom treatment with trastuzumab is unacceptable or no longer desirable, especially if an oral alternative is available, e.g. those with difficult venous access, those who have received multiple lines of trastuzumab containing regimens or who would rather receive an all-oral combination. In these circumstances lapatinib would be a clinically appropriate and much less costly alternative to trastuzumab.	
GSK	*Additional considerations* Lapatinib plus capecitabine offers the convenience of an all-oral regimen which can be self-administered by the patient at home, reducing time spent in hospital and the expense and inconvenience of hospital attendance, when compared with intravenous therapies. The importance of being able to spend time outside of hospital with family and friends cannot be overestimated for these patients whose life expectancy is short. The current recommendation is inconsistent with NHS policy of patient choice and of care closer to home - both of which would be provided by lapatinib. Lapatinib represents an innovative approach to cancer treatment for several reasons, including: - Selective targeting of both the epidermal growth factor receptor 1 (EGFR, ErbB1) and HER2 (ErbB2) receptors; - Small molecule which can bind intracellularly, and with the potential to cross the blood brain barrier unlike large monoclonal antibodies;	The Committee considered the wider benefits that may be associated with lapatinib. These include providing treatment choice and the fact that lapatinib is taken orally, reducing time spent in hospital and the burden of hospital attendance. The Committee was also mindful of the innovative nature of lapatinib, being a small molecule of novel mechanism of action with the potential to cross the blood-brain barrier unlike monoclonal antibodies such as trastuzumab. However, the Committee was not persuaded that the benefits associated with the mode of administration of lapatinib, innovation or the importance of patient choice should alter their decision about lapatinib being an appropriate use of NHS resources. See FAD section 4.17.

Consultee	Comment	Response
	- Oral formulation.	
GSK	*Conclusion* For this very small group of relatively young women with terminal illness, the additional time without disease progression and the extension to survival afforded by lapatinib can be disproportionately valuable to them and their families. We believe that taking into account all the above points in their entirety, rather than each in isolation, lapatinib when considered under the end of life guidance is a valuable option for use on the NHS. Furthermore, as it is the only HER2-targeted option for those who have progressed on trastuzumab exclusively outside the brain we urge the Committee to consider lapatinib as an option for medicine for the eligible population, in view of its 'end of life' status. At the very least with application of the TPAP, lapatinib represents an effective and much less costly clinically valuable alternative for those patients who have progressed in the brain and for whom intravenous trastuzumab, which is recommended as an appropriate treatment in the advanced breast cancer guideline, is no longer desirable. We suggest that NICE consider this sub-group specifically in the context of this consultation.	Comments noted. See responses above.
GSK	**Are there any equality related issues that need special consideration that are not covered in the ACD?** We do not believe that there are equality related issues needing special consideration which have not been highlighted in previous submissions and consultations. ***References included but not reproduced***	Comment noted. No actions required.
Royal College of Physicians (RCP)	I write on behalf of the NCRI Breast Clinical Studies Group/RCP/RCR/ACP/JCCO with relation to the above. We are grateful for the opportunity to comment and would like to make the following joint response.	Comment noted. See responses below.

Consultee	Comment	Response
RCP	There would seem to me to be some incontrovertible conclusions from the available data: (a) there is clear evidence of the efficacy for the addition of Lapatinib to Capecitabine in patients with advanced, HER2-overexpressing breast cancer previously treated with Herceptin and chemotherapy [n=399]. The demonstrated efficacy is in terms of an improvement in time to progression and response rate. The trial was not primarily designed to measure either the overall survival benefit, nor the cost-effectiveness of the intervention, so that data on these two aspects are necessarily much less certain	The evidence from the lapatinib trial EGF100151 has been considered by the Committee and is presented in the FAD. The Committee recognised that the trial was not primarily designed to measure overall survival or cost-effectiveness. See FAD sections 3.2-3.2, 3.20 and 4.5.
RCP	(b) there is also further evidence from randomised trials to support the use of continued anti-HER2 therapy after progression on Trastuzumab (when Trastuzumab is combined with Capecitabine: GBG-26 trial [n=156]; and when combining Lapatinib and Trastuzumab as compared to using Lapatinib monotherapy – EGF104900 trial, [n=296]	The evidence from the GBG26 trial has been considered by the Committee and is presented in the FAD. See FAD sections 3.7 and 4.11.
RCP	(c) there is a clear unmet need for this patient population with generally poor outcomes, as demonstrated by the median survivals of patients in both the pivotal Lapatinib trial and the German GBG trial not given further anti-HER2 therapy being less than 24 months from time of entry into the study. The unmet need is because there are no randomised trials of which I am aware that demonstrate superiority for any other intervention in this subgroup of breast cancer patients.	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 4.17 - 4.23.
RCP	Patients enrolled in these studies were of good performance status, and are similar to many candidate patients treated in the NHS at present: living independent and fully functional lives including full-time employment, caring for relatives etc. Thus their burden on the state health care (and social care systems) will significantly increase when their disease is less well controlled.	Comment noted. No actions required.
RCP	Thus it would seem that the two questions that NICE has had to address are: (a) what is the best estimate of the cost/QALY for adding Lapatinib to	Comment noted. The Committee has considered the estimate of cost effectiveness of adding lapatinib to capecitabine provided by the manufacturer of lapatinib. See FAD

Consultee	Comment	Response
	Capecitabine in patients progressing after chemotherapy and Trastuzumab	sections 4.9 and 4.10.
RCP	(b) is that cost something that the NHS should bear, given the resource constraints, noting that NICE is NOT asked to consider this instead of any other medical intervention for breast cancer or any other condition.	Comment noted. The Institute is asked to take account of the overall resources available to the NHS when determining cost effectiveness. Therefore, decisions on the cost effectiveness of a new technology must include judgements on the implications for healthcare programmes for other patient groups that may be displaced by the adoption of the new technology. See the guide to the methods of technology appraisal section 6.2.13.
RCP	This NICE STA is not structured to draw any conclusions about the cost-effectiveness of either continued anti-HER2 therapy beyond progression on Trastuzumab, nor in particular for the use of Trastuzumab in that setting. However, there were statements in the FAD about the latter for which the evidence base is thin (only 156 patients in the trial) and no modelling data were made available to those of us accessing the draft FAD.	Comment noted. NICE can only make recommendations according to the marketing authorisation of the technologies being appraised. Therefore the Committee is unable to make recommendations about the use of trastuzumab at this point in the care pathway. However, the Committee has to make judgements on the appropriateness and relevance of comparator technologies because this is crucial to the consideration of the cost-effectiveness evidence. See the guide to the methods of technology appraisal section 6.2.16.
RCP	The UK population eligible for using Lapatinib fall into three groups in my view, based on current clinical practice and the trial data: (a) patients progressing for the second+ time after anti-HER2 therapy (usually Trastuzumab). These patients were represented by only 1/3 of the patients in the Lapatinib trial but none of those in the GBG trial. In these patients the addition of Lapatinib resulted in smaller improvements in PFS (HR = 0.64, p = 0.09) but no evidence for any difference in overall survival	The Committee has considered the subgroup data based on number of trastuzumab regimens previously received in the metastatic setting. The Committee considered that the subgroup data showed inconsistent results that made it difficult to interpret. Therefore although it may be considered hypothesis generating, it was not appropriate to use it to form the basis of recommendations. See FAD sections 3.22

Consultee	Comment	Response
		and 4.22
RCP	(b) patients progressing/relapsing for the first time on Trastuzumab who would in the NHS get further Trastuzumab. Survey data produced by NHS clinicians independently of any pharmaceutical company (previously supplied to NICE) suggests that as much as 50% of the population of patients progressing on Trastuzumab in the NHS may be offered further Trastuzumab. In these patients the best estimates suggest little difference in either efficacy (cross-trial comparison) OR cost-effectivenesss (NICE's own calculations) between these two strategies. There are practical advantages for each: there may be compliance problems with oral Lapatinib, and for some patients the continued administration of Trastuzumab intravenously requires significant travel to a hospital and/or insertion of a semi-permanent indwelling intravenous cather with associated risks and health care costs.	The Committee was not persuaded that the analyses comparing lapatinib with trastuzumab formed an appropriate basis for deciding the cost effectiveness of lapatinib. See FAD sections 4.13, 4.24-4.27. The Committee considered the wider benefits that may be associated with lapatinib but was not persuaded that the benefits associated with the mode of administration of lapatinib, innovation or the importance of patient choice should alter their decision about lapatinib being an appropriate use of NHS resources. See FAD section 4.17.
RCP	(c) patients progressing/relapsing for the first time on Trastuzumab who would in the NHS get NO further anti-HER2 therapy – these patients make up 2/3 of those women enrolled into the Lapatinib study and 100% of those enrolled into the GBG study. Survey data suggest they may represent at least ½ of patients in the NHS progressing on Trastuzumab. In both studies, this group demonstrated statistically significant benefits for further anti-HER2 therapy, with HRs for PFS of 0.5 for the addition of Lapatinib to Capecitabine and 0.69 for the administration of continued Trastuzumab in combination with Capecitabine. There were also statistically significant improvements in response rates (for which there are data from other studies demonstrating that this usually results in improvements in Quality of Life), and clinically significant improvements in Overall Survival in this population (medians improving from 51 to 74 weeks, p = 0.08 for Lapatinib and from 20 to 25 months with Trastuzumab, p = 0.26). Thus whilst neither trial is significant for survival gains alone, neither trial was designed to address this question, and *any* estimates of the cost/QALY gained are therefore necessarily only crude approximates. Given the observed differences in median survival in a group of patients half of whom will have died within 2 years, these data would seem to be eligible for the new "end-of-life" approach by NICE.	The Committee considered the exploratory subgroup data provided by the manufacturer of lapatinib to support the benefits observed in the clinical trial. The Committee considered that the subgroup data showed inconsistent results that made it difficult to interpret. Therefore although it may be considered hypothesis generating, it was not appropriate to use it to form the basis of recommendations. See FAD sections 3.22 and 4.22. The Committee considered the cost effectiveness analysis provided by the manufacturer for the whole trial population that compared lapatinib plus capecitabine with capecitabine alone. The Committee considered this analysis within the context of the supplementary advice from the Institute to be taken into account when appraising treatments which may be life extending for patients with

Consultee	Comment	Response
		short life expectancy. See FAD sections 4.18-4.23.
RCP	There would seem to be little or NO evidence to support access to Lapatinib for patients in group (a). However, for patients in group (b), the data presented by NICE find no significant efficacy or cost differences, so it would seem logical that for patients in this group, in the NHS, access to Lapatinib is as reasonable as access to Trastuzumab, in that there are very few if any cost implications for the NHS when choosing between anti-HER2 therapy. NICE might argue that continued Trastuzumab is not Licensed, and neither is the use of Lapatinib in only a sub-group of patients: but as we all know, there are many unlicensed treatments given in the NHS which may have LESS robust supporting evidence than the use of continued anti-HER2 therapy, for which question over ***800*** patients worldwide have been enrolled into randomised phase II/III clinical trials.	Comment noted. The Committee was not persuaded that the analyses comparing lapatinib with trastuzumab formed an appropriate basis for deciding the cost effectiveness of lapatinib. See FAD sections 4.13, 4.24-4.27.
RCP	For patients in group (c), the available data strongly suggest clinical efficacy in terms of response rate, progression-free and overall survival, in a patient group that meets the revised criteria for "end-of-life" drugs in the NHS: - median survival less than 2 years - improvements in survival of the order of 3-4 months no other proven therapies given that there are no other randomised trials demonstrating superior efficacy for one therapy or another in this sub-group of HER2 positive, Trastuzumab-exposed patients. The creation of this "route" for NICE recommendation for NHS use was created in response to recognition that the UK public is prepared to spend more to help these patients than some other patient groups. I am not aware of any evidence that the public is less prepared to spend the increased cost/QALY in this particular patient group just because, having breast cancer, they have already benefited from active therapies in contrast to patients with other cancers that have less effective therapies. It might be argued that this conclusion is based on a hypothesis-generating subgroup analysis of patients in the Lapatinib trial, but it needs to be recalled that this patient group is not only larger than the GBG026 trial, but is also larger than the number of patients in the subgroup which formed the basis of	The Committee considered the cost-effectiveness analyses provided by the manufacturer under the supplementary advice on end of life. The Committee considered that the magnitude of additional weight that would need to be assigned to the QALY benefits for the base-case ICER of £59,400 per QALY gained to fall within the current threshold range was not acceptable. Therefore, the Committee concluded that lapatinib as a treatment for women with previously treated advanced or metastatic breast cancer would not be a cost-effective use of NHS resources. See FAD section 4.23.

Consultee	Comment	Response
	the first registration of Trastuzumab in metastatic breast cancer, an analysis that was also an unplanned, subgroup analysis (using only HER2 3+ and taxol treated patients)! Furthermore, since even the full dataset of patients in the Lapatinib trial was inadequately powered to demonstrate the likely differences in overall survival, drawing conclusions about differences in Overall Survival from either this large subset, or the full trial dataset, are similarly unreliable.	
RCP	We therefore find NICE's rejection of the use of Lapatinib in patients progressing for the first time on Trastuzumab inconsistent with its own "end-of-life" criteria, and deprives some (but not all) eligible patients in the NHS of the option of further effective therapy that is very likely to make a difference to their overall quality of life, contribution to society and survival.	Comment noted. See responses above.
Department of Health	Thank you for the opportunity to comment on the Appraisal Consultation Document and Evaluation Report for the above single technology appraisal. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	Comment noted. No actions required.
Welsh Assembly Government	Thank you for giving the Welsh Assembly Government the opportunity to comment on the above consultation. We have no comments to make at this stage.	Comment noted. No actions required.
Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care and Macmillan Cancer Support	Thank you for the invitation to comment on the post-appeal appraisal consultation document regarding the use of lapatinib for women who have been previously treated for advanced or metastatic breast cancer. Having reviewed the consultation document and evaluation report, Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care and Macmillan Cancer Support have jointly concluded that we have no additional evidence to submit to the Appraisal Committee in relation to our previous responses.	Comment noted. No actions required.
Breakthrough Breast Cancer, Breast Cancer Campaign, Breast Cancer Care and Macmillan	We are disappointed that lapatinib has not been approved for the treatment of women with advanced or metastatic breast cancer whose tumours over-express HER2. As patient organisations, we would like to take this opportunity to once again emphasise how important it is to offer patients greater treatment choice, especially for patients with metastatic disease who often have limited treatment options.	Comment noted. The recommendations are based on evidence of both clinical and cost effectiveness. In addition, the Committee considered the wider benefits of lapatinib treatment including the availability of treatments for patients with metastatic disease. See FAD section 4.17

Consultee	Comment	Response
Cancer Support		
Royal College of Nursing	Nurses working in the breast care and oncology area of health have reviewed 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. There are no further comments to make on this document on behalf of the Royal College of Nursing. Thank you for the opportunity to review this document.	Comment noted. No actions required.
Royal College of Pathologists	The Royal College of Pathologists have not comments to make at this stage of the development.	Comment noted. No actions required.

Comments received from commentators

Commentator	Comment	Response
Roche	Thank you very much for the invitation to comment on the lapatinib ACD. At this time and after reviewing all the relevant documentation, we have no further comments to add to those previously provided by Roche during this appraisal process.	Comment noted. No actions required.

No web comments received