NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Lapatinib or trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2

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

Definitions:

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

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

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
GlaxoSmithKline	Our comments on the ACD are structured below in response to the specific questions posed by NICE. 1. Has all of the relevant evidence been taken into account? GlaxoSmithKline considers that the ACD does take into account the relevant evidence	Comment noted, no response required.
GlaxoSmithKline	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? We believe that the summaries of the clinical and cost-effectiveness of lapatinib plus an aromatase inhibitor are not reasonable interpretations of the evidence. We have identified a number of issues with the economic evaluation conducted by the Assessment Group, which have a direct impact on the interpretation of the clinical and the cost-effectiveness evidence and potentially affect the most plausible ICER range quoted by the Appraisal Committee in the ACD. A summary of these issues is provided below, with specific details provided in our comments on the executable model for lapatinib (GSK pro-forma response).	Please see responses to each part of this comment below.
GlaxoSmithKline	1.1. Clinical Evidence The outcomes benefit (QALYs gained) calculated in the Assessment Group economic evaluation implies a difference in effectiveness between lapatinib and trastuzumab that is not supported by the available clinical evidence in the patient population under consideration. In assessing the likely long term survival benefit derived from clinical interventions, extrapolation of clinical trial benefits is required. The resulting projected survival estimates allow HTA bodies to make inferences of the long-term treatment effects on quality-of-life-adjusted survival. Our main concern in this particular MTA is the fact that different modelling techniques and assumptions have been applied to assess the long-term benefit of lapatinib plus letrozole relative to those used for trastuzumab plus anastrozole. It can be stated that the use of dissimilar approaches is not only likely to yield different results, but more importantly it might prevent the Appraisal Committee from making a comparable comparison when analysing the presented data. The Assessment Group (AG) has chosen to model clinical benefit from the PFS curves using different methodologies for the EGF30008 and TAnDEM clinical trials (Johnston et al. 2009; Kaufman et al. 2009). For the EGF 30008 trial, the method used by the AG assumes that no further benefit accrues to the patients who remain on lapatinib after 16 months, whilst for TAnDEM it is assumed that the benefit continues. The binary differentiation in methods is based on whether the Kaplan Meier curves for the intervention and comparator intersect at the tail. The number of patients contributing to the PFS curves by 16 months for both EGF 30008 and TAnDEM is small. At 15 months the number of patients at risk is 20 for lapatinib plus letrozole, 18 for placebo plus letrozole, 17 for trastuzumab plus anastrozole and 9 for anastrozole alone (Johnston et al. 2009;	Comment noted. Please see FAD section 4.3.8. The Committee concluded that the manufacturer's estimate of progression-free survival was acceptable.

Consultee	Comment	Response
	Kaufman et al. 2009). The modelling methods used by the AG assume that all data points along the Kaplan Meier plots demonstrate statistically significant differences between the clinical benefit afforded by the intervention arm vs the placebo/comparator arm. It seems clinically unintuitive to assume that one drug suspends all benefit after 16 months and the other retains a benefit, when: a) The median PFS benefit of lapatinib plus letrozole is numerically higher and in all likelihood clinically comparable to that of trastuzumab plus anastrozole. b) The modelling approach taken by the AG for lapatinib leads to a predicted OS curve that has a poor fit and underestimates the empirical overall survival data generated to date for lapatinib plus letrozole by approximately 44% (NICE 2010b page 170; GSK comments on the Assessment Report). It should be noted that the overall survival (OS) data for EGF 30008 is not yet mature. At the time of the last data cut (3rd June 2008), 47% of deaths had occurred. The current OS data indicate a one month survival advantage for the patients taking lapatinib plus letrozole over those taking placebo plus letrozole (33.2 vs 32.2 months), although the result does not reach significance (HR=0.74; 95% CI, 0.5 to 1.1) and the data is influenced by lines of therapy subsequent to progression.	
GlaxoSmithKline	**1.2. Cost-effectiveness Evidence** **Errors in the probabilistic sensitivity analysis** Information from the lapatinib executable model provided by NICE suggests that there are errors in the calculation and a flaw in the methodology applied to the probabilistic sensitivity analysis (PSA). These have an impact on the plausible incremental cost effectiveness ratio (ICER) range quoted in the ACD for lapatinib plus letrozole. Typically in a cost-effectiveness acceptability curve (CEAC) presentation of the PSA data, the curves for the intervention and the comparator cross at a point approximating the estimated base-case ICER value. For the comparison of lapatinib plus letrozole versus letrozole monotherapy, the Assessment Group's base-case estimate (as quoted in the model) is £215,504 per QALY gained (for a 20 year time horizon). The point at which the CEACs cross is, however, above £2,000,000 per QALY gained. While it is possible for the CEAC to cross at points above or below the base-case, a discrepancy of this magnitude is highly suggestive of an error in the PSA. It should be noted that the estimated mean QALY for lapatinib plus letrozole from the PSA is 1.4806, compared with the base case estimate of 1.5813 QALYs. This results in an incremental PSA QALY value of 0.01 instead of a value closer to the base case estimate of 0.12. This approximately 12-fold discrepancy in the QALY estimate results in a corresponding inconsistency in the average ICER (approximately £215,000 versus approximately £2,500,000 per QALY gained). The source of the discrepancy between the mean PSA sampled value of the QALYs for lapatinib plus	The Committee considered the ICERs for lapatinib. The Committee considered that the Assessment Group's estimates were likely to be an over-estimate of the most plausible ICER for lapatinib on the basis of previous discussions in which the Committee had agreed that the progression-free survival had been under-estimated by the Assessment Group (see FAD section 4.3.10).

Consultee	Comment	Response
	letrozole compared with the base case estimate of the QALYs for lapatinib plus letrozole is an error in sampling of the decrement in utility with diarrhoea and vomiting. As a consequence of this error is the 'mean' incremental QALYs for lapatinib plus letrozole versus letrozole in the PSA is underestimated by approximately 90% and the ratio of the mean incremental costs to the mean incremental QALYs with lapatinib plus letrozole versus letrozole (labelled as "Overall IC/IQ") is overestimated by a factor of more than 10-fold. The resulting CEAC and the scatter-plot for the incremental QALYs versus incremental costs are thus incorrect as is the data in Table 28 of the Assessment Report. Further details of this sampling error and other errors in the PSA are provided in the GSK pro-forma response document for the lapatinib model. In addition to the issues above, it should be noted that the ratio of the average PSA costs and average PSA QALYs has been calculated instead of the average PSA ICER. There is however a fundamental mathematical difference between these two types of calculations which provide different information and produce different results. Specifically, the ratio of the average incremental costs to the average incremental QALYs weights each simulation by the incremental QALYs. Presumably, all simulations should be weighted equally, and the ratio of the average incremental cost to the average incremental QALYs may be subtly biased (depending on the correlation of the ICER with the incremental QALYs) when compared with the average of the ICERs. For the comparison of lapatinib plus letrozole versus letrozole monotherapy some of the simulations in the Assessment Group model fall into different quadrants of the cost -effectiveness plane which means that some have negative ICER values. It is therefore not appropriate to calculate an average PSA ICER for lapatinib plus letrozole. GlaxoSmithKline understand the possible rationale for the methodological approach adopted by the Assessment Group but questions the validity of using the ratio of the average PSA costs and average PSA QALYs.	
GlaxoSmithKline	**Lack of consistency in the base case and the PSA estimates reported in the Assessment group report, the model and the ACD.** In the Assessment Report the PSA ICER was given as £2,895,994 per QALY gained; in the model the value appears to be £2,494,432 and in the ACD report the figure quoted is £960,800. With regard to the base case ICER (for the 20 year time horizon) a value of £220,626 per QALY gained is given in the Assessment Report whilst in the model the estimate appears to be £215,504 per QALY gained. There is however a calculation error on the 'LET' sheet of the model which if corrected produces an ICER of £225,962. It appears that the reason for the difference between the results in the model and the Assessment Report relate to differences in the utility values used for PFS for lapatinib plus letrozole and letrozole. No explanation for this difference is provided and therefore it is difficult to ascertain which of the two sets of estimates is more appropriate. Further details of this issue are provided in the GSK pro-forma response document for the lapatinib model.	Comment noted. The Committee noted that following consultation the Assessment Group provided a revised estimate of £228,900 per QALY gained for the mean probabilistic ICER (see FAD section 4.3.10).

Consultee	Comment	Response
GlaxoSmithKline	**Lack of transparency in the Assessment Group modeling** The AG model has relatively little documentation of the model inputs and results which limits transparency and makes it difficult to conduct a thorough review of its robustness and reliability. For example, it is difficult to assess the methods by which the PSA values were calculated and whether the PSA values quoted in the Assessment Report are from the use of the 'standardized' or 'un-standardized' PSA approach. Further information transparency issues with the model are given in the GSK pro-forma response document for the lapatinib model.	Comment noted. The Assessment Group were asked to respond to each issue raised on the model. Their response is included in the evaluation report.
GlaxoSmithKline	**Questionable face validity of OS data generated by AG model** The AG model does not reflect the actual OS data from the EGF30008 clinical trial. As previously reported (NICE 2010b page 170), GlaxoSmithKline estimated that the AG model underestimates the OS gain achieved with lapatinib plus letrozole versus letrozole. This underestimation is approximately 44% based on a comparison of the AG modeled data with the Kaplan-Meier curves from the EGF30008 clinical trial up to the end of the 46 month follow-up period. The reasons for the discrepancy between the AG model projections and the empirical survival distributions are uncertain. All of the issues highlighted above call into question the robustness of the data analysis upon which NICE has based its provisional recommendation.	Comment noted. The Committee heard from the Assessment Group that because the curves for the treatment and comparator arms in EGF30008 converged, the modelling carried out in their model may have under-estimated the longer term progression-free survival gain with lapatinib. The Committee therefore concluded that the manufacturer's estimate of progression-free survival was acceptable.
GlaxoSmithKline	**2. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** GSK believe that whilst resolution of the issues described in point 2 above might not affect the provisional recommendation, the detail underlying this recommendation in the ACD does not reflect the true clinical and cost-effectiveness of lapatinib plus an aromatase inhibitor in the first line treatment of women with metastatic hormone-receptor-positive/HER2+ breast cancer, and should be reassessed and corrected.	Comment noted. The Committee were not satisfied that the additional benefit of treatment with lapatinib plus an aromatase inhibitor justifies the cost of treatment to the NHS.
Roche	**1.1 Concerns identified in review of the AG economic model** The Committee considered the AG cost-effectiveness estimate to be the upper range of the plausible ICERs for trastuzumab in combination with anastrozole. Roche have attempted to review the AG economic model, but have struggled to assess its internal validity due to a number of 'hard coded' values (i.e. values not derived from formulas presented in the Excel spreadsheets) and the lack of detailed technical documentation of the methods employed. Despite this difficulty, we believe we have	The Assessment Group were asked to respond to each issue raised on the model. Their response is included in the evaluation report.

Consultee	Comment	Response
	identified some concerns with the AG model.	
Roche	**1. Extrapolation of PFS and the associated drug cost for trastuzumab** To understand the differences between the Roche and AG estimates of the cost-effectiveness of trastuzumab, a comparison of the costs and effects across these two models have been broken down in Table 3 and 4 below. (Tables not reproduced here) From Table 4 above, it is clear that the estimate of time in PFS differs considerably between the Roche original model (1.19 years) and the assessment group's model (1.30 years). In the Roche model, we have utilized the Kaplan Meier PFS curves for both the trastuzumab arm and anastrozole arm from the TAnDEM trial. This data was complete (i.e. no patients remained in PFS at the end of follow-up) and therefore no extrapolation was conducted. It can be considered that the mean time in PFS presented in our model reflects the mean time observed in the clinical trial. In the AG model, it is explained that "the mean progression-free survival was calculated using the Kaplan–Meier area under the curve estimate up to the last recorded event in each group, and then adding the area under the projected long-term Weibull curve." (section 4.2.14 of the ACD). This method employed by the assessment group seems overly complex, given that no extrapolation should be required if the data is complete This method is in conflict with the method employed by the same AG in a recently published Assessment report on erlotinib in non-small cell lung cancer, where the AG have stated that, in the pivotal trial, no patients remained alive without disease progression at the close of the trial (i.e. the PFS data set is complete) and "in such situations there is no justification for resorting to projective modelling to establish the mean duration of PFS. The most appropriate and reliable measure may be derived directly from a Kaplan-Meier survival analysis" (Bagust, 2010). In addition, the methods used in deriving the Weibull curve were not clearly presented and it is unclear as to whether estimates of uncertainty around their parameter estimates were incorporated into the PSA performed. This also raises doubt into the validity of these results, given that the resulting time in PFS is clearly greater in the AG model than the Roche model which reflects the data available from the TAnDEM trial. The impact of this potential overestimation of time in PFS in the AG model will affect multiple parameters in the model, but the most considerable impact of this overestimate as it relates to the ICER will likely be the overestimation of the cost of trastuzumab and anastrozole combination therapy which is given until disease progression. As shown in Table 3, the cost of the trastuzumab and anastrozole combination therapy is estimated to be approximately £6,500 greater in the AG model (£31,272) compared to the Roche model (£24,774). Indeed, this drug cost of £31,272 is well above the average drug cost which would be expected in this setting, even compared to the average drug cost estimated in the background section of the ACD (£26,832 in ACD section 3.6).	Comment noted. The Assessment Group were asked to respond to each issue raised on the model. Their response is included in the evaluation report.
Roche	**2. Estimation of Overall Survival**	Comment noted. See FAD

Consultee	Comment	Response
	The AG has also employed their own method for calculating overall survival (by independently estimating post-progression survival and summing this figure with PFS) as well as its own method for adjusting for cross-over. Roche believe that utilizing one of the published statistical methods for adjusting for cross-over, which has also been accepted by NICE in formulating positive guidance on a previous technology appraisal (NICE TA179) should be considered the more appropriate of the two approaches for estimating overall survival in the presence of cross-over in a clinical trial. Irrespective of the method used to adjust for cross-over, Roche have further concerns regarding the methods used by the AG to calculate the post-progression survival estimate from inspection of their economic model. In the ACD section 4.2.15, it is explained that in the AG model, "the estimate for overall survival was obtained by combining estimates of mean progression-free survival and mean post-progression survival in each group, and adjusting for the patients who died at or before progression (5.8% in the anastrozole alone group and 9.3% in the trastuzumab plus anastrozole group)". In the TAnDEM trial, 6 patients in each treatment arm died at or before disease progression. Given that there were 103 patients in the intervention arm and 104 patients in the control arm, it would appear that the anastrozole figure was calculated correctly (5.8%) but the proportion in the trastuzumab arm has been overestimated (97/103 = 5.8%). When changing the incorrect cell within the AG model (Sheet TA_AI, cell AO41), this results in a sizable decrease to the ICER (**from £73,135 to £69,514**) resulting from an improved mean time in PPS determined from the trastuzumab arm. In order to provide a crude calculation of the impact of potentially overestimating average time in PFS and therefore overestimating the cost of trastuzumab by £6,500, we have removed an additional £6,500 from the numerator of the AG modified ICER, resulting in a downwards shift of the ICER **from £69,514 to £57,591**. If the Committee were to consider that the methods employed by Roche to adjust for cross-over are more appropriate than the methods used by the AG, then it is plausible that the AG ICER would reduce to similar values as those presented by Roche in our new base case estimate (presented in section 1.2 below). Upon review of the above mentioned 'adjustment factor', it was identified that the AG has also made a second 'Reconciliation adjustment' which is hard-coded into the model at a value of 1.045886595. Whilst there may be justification for this further adjustment, this component of the estimation of post-progression survival has not been documented in the Evaluation Report. In principle, we believe that all elements of the AG model should be fully explained and transparent if the resulting ICERs form part of the Committee's consideration as to the plausible range of ICERs for trastuzumab.	sections 4.3.12 and 4.3.13. The Committee accepted the manufacturer's estimate of progression-free survival for trastuzumab. The Committee concluded that the likely impact on post-progression survival with trastuzumab was most likely to be nearer to zero than either a positive or negative increase.
	1.2 Cost per QALY estimate for trastuzumab The Committee has concluded that the most plausible ICER for trastuzumab plus anastrozole compared with anastrozole alone was likely to be between £54,300 and £73,100 per QALY gained	Comment noted.

Consultee	Comment	Response
	which represents Roche and the Assessment Group (AG) estimates of the cost-effectiveness of trastuzumab in this setting respectively. We discussed above the reasons we believe that the AG's estimates represent an overestimation of the cost-effectiveness of trastuzumab. We have considered the critique from the AG and the Committee and have adapted our economic model to reflect what is considered to be the most appropriate input parameters and comparators. We therefore present below our updated base case analysis based on the following changes: We have assigned the utility values deemed most appropriate by the AG based on the published literature. Different utility values for progression-free survival were assigned to the trastuzumab plus anastrozole group (0.769) and to the anastrozole alone group (0.764). A health state utility value of 0.496 was assigned to the post-progression survival state (ACD section 4.2.17). The AG have justified this choice relative to our original base case utility scores on page 73 of 127 in the Assessment Report. We have removed the indirect comparison and focused explicitly on the trial-based comparison of trastuzumab + anastrozole versus anastrozole monotherapy as considered appropriate by the Committee at this stage of the appraisal (ACD section 4.3.7). Table not reproduced here This update results in the following cost-effectiveness estimates: Cost per Life Year gained = £36,174 Cost per QALY gained = £50,975	
Roche	***1.3 Trastuzumab should be considered under the End of Life criteria*** The Committee concluded that trastuzumab does not qualify for consideration under NICE's supplementary End of Life guidance (EoL) as the size of the population suitable to receive trastuzumab is '*likely to be too high'*. This consideration appears to be founded on the assumption that there are more than 50 patients eligible for treatment in the UK annually and that these 'new' patients would add incrementally to the existing eligible trastuzumab population (7,158) calculated by Roche (ACD section 4.3.14). The conclusion of the Committee appears to be in conflict with the recently published TA208 (for HER2+ gastric cancer) where it was determined that the size of trastuzumab's population was sufficiently small to consider trastuzumab under the EoL guidance. In the following sub-sections we would like to discuss each of these points.	Comment noted. Please see response below.
Roche	**1.3.1 The number of patients eligible for trastuzumab + anastrozole treatment in the UK for the first-line treatment of metastatic HR+/HER2+ breast cancer is approximately 50 per annum** In section 4.3.4 of the ACD it is noted that based upon the '*comments from consultees made during the consultation on the assessment* report' that '*the eligible population is likely to be at least 350 patients per year'*. From this conclusion that Committee determine that the population suitable for treatment with	Comment noted. Please see FAD section 4.3.18 The Committee agreed that the population for whom trastuzumab would be suitable was likely to be more than 50

Consultee	Comment	Response
	trastuzumab in combination with an AI was '*uncertain but likely to be more than 50 patients per year*' (ACD section 4.3.14). We believe that this conclusion is a result of a misunderstanding of the algorithm presented by Roche where the eligible population is broken down further than HER2+/HR+ status. In Table 179 of the Roche submission, we provide a breakdown of the eligible patients for trastuzumab in combination with an aromatase inhibitor. If one was only to use this algorithm to determine the annual incidence of metastatic breast cancer which is both HER2+ and HR+, we would estimate this figure to be greater than 1,300 patient annually (more than the number proposed in the consultee comments on the Assessment report from the Royal College of Physicians of approximately 1,000 patients). However, it must be remembered that the scope of this appraisal is for post-menopausal patients for whom chemotherapy is unintended, within the licensed indication of trastuzumab (which further excludes patients who have received adjuvant trastuzumab and those with CV comorbidities). When these further adjustments are taken into account, the total eligible population is accurately reflected at 50 patients per annum. Please see Table 179 in our original submission for full details.	women per year and possibly as many as 2000 women per year. The Committee concluded that the potential cumulative population covered by the trastuzumab licence would be more than 7000 and possibly up to 9100 people, and that therefore trastuzumab did not fulfil the small population criterion.
Roche	**1.3.2 Patients eligible for trastuzumab + anastrozole have already been incorporated in the 7,158 cumulative eligible patients for trastuzumab** In the mBC algorithm submitted by Roche to calculate the cumulative eligible trastuzumab population in support of consideration on the EoL criteria (Appendix 2, p339 of the original Roche submission), the number of metastatic breast cancer patients eligible for treatment is simply reduced by 5.5% (the percentage of HER2+ mBC patients expected to have cardiac co-morbidities rendering trastuzumab unsuitable (either MI or angina) as found in the Q4 2007 Genactis Breast Cancer Patient Record Survey) in order to conservatively estimate the number of mBC patients suitable for treatment with trastuzumab. Therefore, this calculation of the total eligible mBC trastuzumab population (2,333 patients) does not distinguish between those who will receive trastuzumab in combination with chemotherapy from those who will receive it in combination with an aromatase inhibitor. As a result, the patients under consideration in this appraisal have already been incorporated into the cumulative eligible patient calculation for trastuzumab.	Comment noted. Please above response.
Roche	**1.3.3 The cumulative eligible trastuzumab patient population has not changed since the publication of TA208 and may be considered an overestimation in both appraisals** The conclusion that trastuzumab does not meet the EoL criteria in this appraisal appears to be in conflict with the conclusion reached by NICE Appraisal Committee C in NICE TA208 (trastuzumab for the treatment of HER2+ metastatic gastric cancer (mGC)). In TA208 it was determined that the size of trastuzumab's population was sufficiently small to consider trastuzumab under the EoL guidance. There have been no additions to trastuzumab's marketing authorization since the TA208 guidance was	Comment noted. Please see above response.

Consultee	Comment	Response
	issued in November 2010 and it should be clarified that this 'new' indication has existed in the marketing authorization for trastuzumab since 2006 and is already incorporated in the estimate of patients licensed to receive trastuzumab (7,158) calculated by Roche. The Roche mBC algorithm described above makes no reference to a patient's eligibility for trastuzumab's partner therapies and only removes those patients who would be unsuitable to receive trastuzumab for any of its mBC indications (be that in combination with an AI or taxane). If the algorithm were to be extended to remove those patients unsuitable for either a taxane or an AI the patient pool estimated to be suitable for trastuzumab would fall further. In addition, the incidence of metastatic breast cancer is expected to reduce further in the future as a result of the decreased recurrence of disease due to the uptake of adjuvant trastuzumab treatment (Weisgerber-Kriegl, 2008). Given the above, we would ask the Committee to reconsider the eligibility of trastuzumab for special consideration under the End of Life guidance. If trastuzumab was considered to have a 'small' population in TA208 and that previous determination was likely based on an overestimation of the cumulative population due to the nature of the mBC algorithm presented, it would appear that trastuzumab should be considered to also have a 'small population' in this appraisal.	
Roche	Roche have identified a number of inaccuracies in the summaries provided in the ACD. Section 2.4: It is stated that approximately 30% of people with metastatic breast cancer have HER2+ tumours. This is an overestimation of the more commonly accepted HER2+ figure of 23% which was provided in our original submission (Dybdal, 2005). Section 2.5: It is stated that survival is shortened by up to 50% in people with HER2+ metastatic breast cancer (relative to those with HER2-negative breast cancer). It should be clarified that this shortened survival occurs "in the absence of HER2-targeted therapy" as clinical trials have demonstrated the significant overall survival benefit achieved when trastuzumab is added to standard treatment (Marty, 2005). Section 4.1.8: The ACD states that "progression-free survival results were presented according to the ITT population, centrally confirmed results (confirmed by a blinded Response Evaluation Committee) and results updated at a later cut-off point (April 2008)." The second set of results ("centrally confirmed results") is incorrectly described. The population with centrally confirmed hormone receptor status was a subgroup presented separately, not a population with centrally confirmed response to treatment. In both groups (ITT and centrally confirmed HR+), the response was evaluated by the investigator and the REC. It should therefore read "Progression-free survival results were presented according to the ITT population and the centrally confirmed HR+ population, and updated results were provided at a later cut-off point (April 2008)."	Comment noted. This section has been amended. See FAD section 2.4 Comment noted. This section has been amended. See section 2.5 Comment noted. This section has been amended. See section 4.1.8

Consultee	Comment	Response
	Section 4.1.9: The same incorrect description of "centrally confirmed response" as mentioned above is presented, this time in relation to the overall survival results. A similar amendment should be provided here.	Comment noted. This section has been amended. See section 4.1.9
	Section 4.1.10: It is stated that in the TAnDEM trial, patients in the anastrozole arm crossed over to receive trastuzumab in combination with anastrozole. This is incorrect as the cross-over only describes the 2nd line treatment with trastuzumab without consideration of whether this treatment was partnered with chemotherapy, hormone therapy, or prescribed as monotherapy.	Comment noted. This section has been amended. See section 4.1.10
	Section 4.1.10: The ACD states that "The Assessment Group commented that no statistical methods were described to address the issue of crossover….". This should instead state "In the TAnDEM trial, no statistical methods were described to address this issue of crossover a priori." The methods implemented by Roche to adjust for cross-over are detailed in our original submission (specifically, a post-hoc rank preserving structural failure time statistical model (Robins and Tsiatis 1991)).	Comment noted. This section has been amended. See section 4.1.10
	Section 4.3.4: As in Section 4.1.10, it is stated that in the TAnDEM trial, patients in the anastrozole arm crossed over to receive trastuzumab in combination with anastrozole. This is incorrect as the cross over only describes the 2nd line treatment with trastuzumab and therefore should only state that patients in the anastrozole arm crossed over to receive trastuzumab.	Comment noted. Following the second appraisal committee meeting, this section has been reworded and this statement is no longer included
	Section 4.3.13: It is stated that the centrally confirmed (overall survival) results of the TAnDEM trial exceeded 24 months, as part of the justification of why lapatinib is not eligible for consideration under the End of Life criteria. As noted above, these are not centrally confirmed results but instead represent a subgroup of the ITT population who had centrally confirmed hormone receptor positive disease. It should be noted that in the control arm of the ITT population, median overall survival did not exceed 24 months and it is confusing why the ACD would refer to a subgroup in order to identify a population with an excess of 24 months overall survival. Furthermore, it has been clearly described that 70% of these patients initiated trastuzumab treatment post-progression, often in combination with chemotherapy, which has been clearly demonstrated in other randomized clinical trials (Marty, 2005) to result in a significant overall survival advantage. Therefore treatment with anastrozole monotherapy without the subsequent trastuzumab would have likely resulted in less than 24 months survival.	Comment noted. Following the second appraisal committee meeting, this section has been reworded and this statement is no longer included
	Section 4.2.16: It is stated "After adjusting for patients who died at or before progression (91% of the total)…". The text in parenthesis should read "(9% of the total)" given that 91% represents the total who survived post progression. Furthermore, we believe that the AG have incorrectly calculated this figure which will be described further in Section 2.2 below.	Comment noted. Following the second appraisal committee meeting, this section has been reworded and this statement is

Consultee	Comment	Response
		no longer included

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Royal College of Nursing	**Has the relevant evidence been taken into account?** The summary of evidence in the document seems comprehensive. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence, and are the preliminary views on the resource impact and implications for the NHS appropriate?** The summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by these patients. The preliminary views on resource impact and implications should be in line with established standard clinical practice. **Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS?** There are no comments to make at this stage on the provisional recommendations. We would welcome guidance to the NHS on the use of this health technology **Are there any equality related issues that need special consideration that are not covered in the ACD?** None that we are aware of at this stage. We would however, ask that any guidance issued should show that equality issues have been considered and that the guidance demonstrates an understanding of issues concerning patients' age, faith, race, gender, disability, cultural and sexuality where appropriate.	Comment noted Comment noted Comment noted Comment noted
Royal College of Physicians	**Has all of the relevant evidence been taken into account?** Yes, within the scope of the appraisal all relevant evidence has been considered. In particular the three RCTs that are directly relevant to the appraisal have been analysed in detail. **Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We continue to be concerned regarding the substantial differences in the estimated cost effectiveness of trastuzumab-anastrozole and lapatinib-letrozole arrived at by the Assessment	Comment noted Clinical specialist opinion on this issue was considered by the Committee and is described in

Nominating organisation	Comment	Response
	Group. Letrozole and anastrozole have no clinically detectable difference in efficacy and whist there is only limited data comparing trastuzumab and lapatinib, it seems unlikely that there is a major difference between these drugs. Therefore intuitively the 2 drug-combinations being evaluated seem likely to have similar efficacy but it seems a radically different cost-effectiveness.	section 4.3.3 The Committee understood from clinical specialists that this would be expected in clinical practice (that is, that there would be no difference in the clinical effectiveness of lapatinib and trastuzumab).
	Are the provisional recommendations sound and a suitable basis for guidance to the NHS? Subject to the cost-effectiveness analysis being considered reasonable, then yes.	Comment noted
	Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief? No	Comment noted
	Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document The principal beneficiaries of lapatinib or trastuzumab in combination with endocrine therapy are likely to be older and less fit patients for whom chemotherapy is a particularly unattractive option. This appraisal leaves the option of trastuzumab in combination with chemotherapy available to all patients. However, the considerations that would have prompted clinicians to recommend endocrine therapy in preference to chemotherapy, combined with lapatinib or trastuzumab to some patients with ER-positive HER2-positive patients are likely to result in lower (less effective) doses of chemotherapy being administered to these patients if the option of HER2-targetted therapy in combination with an aromatase inhibitor is not available. Older less-fit patients are therefore likely to be disadvantaged by the recommendations.	Comment noted.

Comments received from commentators

Commentator	Comment	Response
NHS Quality Improvement Scotland	1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results? Yes 2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations? Agree that not cost effective 3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? Yes they are sound 4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? Yes 5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. NO 6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. NO	Comments noted. The recommendations did not change in the FAD but have been reworded for clarity (see section 1.1 and 1.2)
NHS Quality Improvement	1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do	Comments noted. The recommendations did not

Commentator	Comment	Response
Scotland	you consider has been omitted, and what are the implications of this omission on the results? Yes 1. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations? Yes 2. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? Yes 3. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? Yes 4. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. No 5. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. No 6. Please add any other information which you think would be useful to NICE or helpful in guiding the Scottish response to this assessment This guidance will result in a small number of patients, perhaps 250 – 300 per year in UK, receiving Trastuzumab plus chemotherapy at first relapse, who otherwise may have been offered Trastuzumab or Lapatinib plus an aromatase inhibitor if it were available. This pre-supposes that such patients would be deemed eligible for Trastuzumab plus chemotherapy is case of non-response or failure, but in such	change in the FAD but have been reworded for clarity (see section 1.1 and 1.2)

Commentator	Comment	Response
	event a proportion of patients would be saved chemotherapy completely. Final sentence of section 2.3 is incorrect.	Comment noted. Comments in the literature suggest that the sentence is correct and so it has not been amended
NHS Quality Improvement Scotland	1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results? I agree that the relevant evidence has been taken into account. 2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations? I agree with the summaries being representative of the evidence. 3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? The recommendations are reasonable and provide suitable basis for guidance to NHS. 4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? Yes they are applicable to NHS Scotland. 5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. No. It is not expected to have any impact on current patients' pathway as the standard of care currently includes the use of single agent AI or chemotherapy with Trastuzumab. 6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case.	Comments noted. The recommendations did not change in the FAD but have been reworded for clarity (see section 1.1 and 1.2)

Commentator	Comment	Response
	No. Patients' pathways are generally similar.	
NHS Quality Improvement Scotland	1. Do you consider that all the relevant evidence has been taken into account? If not, what evidence do you consider has been omitted, and what are the implications of this omission on the results? Yes 2. Do you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence? If not, in which areas do you consider that the summaries are not reasonable interpretations? Yes 3. Are the provisional recommendations of the Appraisal Committee sound and do they constitute a suitable basis for the preparation of guidance to the NHS? If not, why do you consider that the recommendations are not sound? Yes 4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland? Yes 5. Would the provisional recommendations change the patient pathways and/or patient numbers in NHSScotland? If so, please describe what these changes would be. No 6. Do you think there is any reason why this provisional guidance would not be as valid in Scotland as it is in England and Wales? If yes, please explain why this is the case. No	Comments noted. The recommendations did not change in the FAD but have been reworded for clarity (see section 1.1 and 1.2)
CSAS/NHS Portsmouth	**Adding lapatinib or trastuzumab to an aromatase inhibitor improves median progression free survival (PFS) but not overall survival.** Single RCTs found that adding lapatinib to letrozole improved median PFS from 3.0 months to 8.2	Comment noted

Commentator	Comment	Response
	months, and that adding trastuzumab to anastrozole improved median PFS from 2.9 months to 5.8 months. Indirect comparisons from the manufacturers found no differences in PFS between these two combination regimens. The RCTs found that the combination regimens did not improve overall survival compared with aromatase inhibitors alone, and indirect comparisons found no difference in overall survival between the combination regimens.	
	Adding lapatinib or trastuzumab to an aromatase inhibitor increases adverse events	Comment noted
	Adding lapatinib to letrozole increased adverse events compared with letrozole alone, including diarrhoea (68% vs 8%), rash (46% vs 8%) and nausea (27% vs 18%; p<0.05 for all three events). Adding trastuzumab to anastrozole increased adverse events compared with anastrozole alone (overall adverse events: 87% vs 65%; serious adverse events; 23% vs. 6%). The most common adverse events with trastuzumab plus anastrozole included fatigue (21% vs. 10%), diarrhoea (20% vs 8%), and vomiting (21% vs. 5%). Lapatinib and trastuzumab have been associated with cardiotoxicity therefore both drugs require cardiac monitoring(left ventricular function) before and during treatment. Liver function monitoring before and during treatment is also recommended with lapatinib.	
	Adding lapatinib or trastuzumab to aromatase inhibitor treatment is estimated to increase lifetime costs by around £26,000 per patient, without an extension tolife	Comment noted
	NICE made these estimations based on acquisition drug costs alone for a mean of 55.2 weeks' treatment, and using British National Formulary 60 costs (excluding VAT)	
	The Appraisal Committee concluded that the plausible ICER for lapatinib plus letrozole compared with letrozole alone was likely to be between £74,400 and £1,000,000 per QALY gained and for trastuzumab plus anastrozole compared with anastrozole alone was likely to be between £54,300 and £73,100 per QALY gained. CSAS is in agreement with the appraisal committee that this far exceeds the thresholds usually accepted as a cost effective use of NHS resources.	
	The exact number of people who would be eligible to receive trastuzumab or lapatinib plus an aromatase inhibitor (if approved) in preference to alternatives is unknown	Comment noted. This information has been discussed by the Committee (See section 4.3.18)
	The best estimate for an average PCT of 300,000 based on a maximum uptake is that they could expect to treat 11 women annually	
	There were limitations to the quality of the research	
	Although the RCTs were of good quality, each combination (lapatinib plus letrozole or trastuzumab plus anastrozole) was only assessed in a single RCT with about 200 women with HER2+ and hormone receptor positive metastatic breast cancer. The populations in these trials were substantially different; therefore the indirect comparisons carried out by the manufacturers should be interpreted with caution.	Comment noted

Comments received from members of the public

Role*	Section	Comment	Response
NHS professional 1	1	NHS Bradford and Airedale strongly support the ACD recommendation that Lapatinib or trastuzumab in combination with an aromatase inhibitor are not recommended as options for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses human epidermal growth factor receptor 2 (HER2). The evidence available shows that these treatments are not affordable or cost-effective, do not increase overall survival or quality of life and are associated with substantial increases in adverse events in patients. Based on the prevalence and cost information provided by NICE, approximately 20 patients per year would be eligible for such treatment were they approved. The increased lifetime costs (just for drug acquisition) if all eligible patients were treated this way would be in excess of £500,000. This spend would need to be found from within the existing budget for breast cancer (approx £4 million in 2008/09) and would therefore result in a loss of existing services.	Comment noted. The recommendations did not change in the FAD but have been reworded for clarity (see section 1.1 and 1.2)
NHS professional 1	3	The potential additional lifetime cost of approximately £26,000 per patient (for mean of 55.2 weeks' treatment) for drugs cost alone, would be result in an equivalent reduction elsewhere in breast cancer services to fund them if approved. In the event that these treatments were approved we would be extremely concerned about the substantial increase in adverse events and serious adverse events observed in both of the trials of lapatinib and trastuzumab added to compared to the use of an aromatase inhibitor alone. Given that both lapatinib and trastuzumab are associated with cardiotoxicity, additional cardiac monitoring before and after treatment would be required at further increased cost. Similarly it is noted that liver function monitoring before and after treatment is recommended for lapatinib which again would have resource implications.	Comment noted
NHS professional 1	4	Although the two RCTs are of high quality the overall evidence base is limited as there is only one relatively small trial for each drug combination. Also, given the substantially different populations recruited we do not feel that the indirect comparisons conducted by the manufacturers were appropriate. The evidence does not demonstrate any increase in overall survival through adding lapatinib and trastuzumab to an aromatase inhibitor. Although modest improvements in PFS were found for both drugs, where quality of life data was reported (only for	Comment noted

* 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*	Section	Comment	Response
		lapatinib) there was not found to be any improvement compared to the use of an aromatase inhibitor alone. Neither laptinib and trastuzumab were found to be cost-effective. The estimated ICERs (£74,000 to £1,000,000, and £54,300 to £73,100 per QALY respectively) were substantially in excess of the recognised thresholds for cost-effectiveness.	
NHS professional 1	5	Based on the prevalence and cost information provided by NICE, approximately 20 patients per year would be eligible for such treatment were they approved. The increased lifetime costs (just for drug acquisition) if all eligible patients were treated this way would be in excess of £500,000. This spend would need to be found from within the existing budget for breast cancer (approx £4 million in 2008/09) and would therefore result in a loss of existing services.	Comment noted
NHS professional 2	1	Agree with the recommendation	Comment noted
NHS professional 2	4	These technologies do not reflect a cost effective use of NHS Resources with ICER for lapatinib plus leptosome compared with letrozole alone was likely to be between £74,400 and £1,000,000 per QALY gained, and for trastuzumab plus anastrozole compared with anastrozole alone was likely to be between £54,300 and £73,100 per QALY gained. Overall survival is not improved, and the combination results in a significant rise in ADRs. The populations in these trials were substantially different therefore the indirect comparisons carried out by the manufacturers should be interpreted with caution.	Comment noted
NHS professional 3	1	Agree	Comment noted
NHS professional 3	3	Costs of Trastzumab need revising to reflect actual costs. For hospital administration VAT should be added. No discounts are available currently for herceptin. Echo costs need inclusion. For Homecare costs, extra costs of compounding, dispensing, delivery and nurse time are added.	Comment noted
NHS professional 3	4	Overall survival was not increased. Yet harms increased. Toxicity (cardio and hepatic) needs to be measured for the effect on quality of life. The QALYs are high above the cost effective threshold and the NHS needs to be equitable. Other breast cancer treatments are available. NHS money will need to be taken from other services to meet the costs of these drugs e.g from patients with other end of life conditions who need support other than drugs e.g. heart failure,	Comment noted

Role*	Section	Comment	Response
		COPD.	
???No role listed	1	I support the view base on the evidence summary presented. the cost of therapy, considering the impact on survival, would seem unsustainable	Comment noted
???	2	We are not aware of a specific need to further augment clinical practice beyond current recommendations	Comment noted
???	3	Adding lapatinib or trastuzumab to aromatase inhibitor treatment is estimated to increase lifetime costs by around £26,000 per patient, without an extension to life.	Comment noted
???	4	In this indication these technologies are not a cost effective use of NHS resources Adding lapatinib or trastuzumab to an aromatase inhibitor improves median progression free survival (PFS), but not overall survival Adding lapatinib or trastuzumab to an aromatase inhibitor increases adverse events There were limitations to the quality of the research: Although the RCTs were of good quality, each combination (lapatinib plus letrozole or trastuzumab plus anastrozole) was only assessed in a single RCT with about 200 women with HER2+ and hormone receptor positive metastatic breast cancer.	Comment noted
???	5	The exact number of people who would be eligible to receive trastuzumab or lapatinib plus an aromatase inhibitor (if approved) in preference to alternatives is unknown. Current expectations would be that an average PCO would treat around 11 patients, giving an incremental cost in excess of £250k with no substantial survival benefits	Comment noted
???	7	We agree with the proposed review date	Comment noted