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 post-appeal 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.
GlaxoSmithKline	**2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** As previously highlighted in our response to the Assessment Report and the first ACD, (NICE 2011a, NICE 2011b) GlaxoSmithKline (GSK) disagrees with the approach to the economic modelling taken by the Assessment Group, which we believe has an impact on the interpretation of the clinical and cost effectiveness evidence reported in this second ACD.	Comment noted. Please see responses to each part of this comment below.
GlaxoSmithKline	**2.1. Clinical evidence and cost effectiveness** The clinical evidence suggests that lapatinib plus an aromatase inhibitor and trastuzumab plus an aromatase inhibitor are of comparable efficacy and this is acknowledged in section 4.3.3 of the ACD which states: *"The Committee noted that the curves showing the percentages of people alive without progression for the treatment arms were similar to each other between the trials. It 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)."* When evaluated on this basis, as in the GSK and Roche economic evaluations, the estimated incremental cost effectiveness ratios (ICERs) for the two are of a similar magnitude (NICE 2010). However the Assessment Group applied different modelling techniques and assumptions to assess the long-term benefit of lapatinib plus letrozole relative to those used for trastuzumab plus anastrozole. This difference in approach was based on the tail end of the progression free survival curves when the number of patients remaining in the clinical trials was small and the data highly uncertain. This approach in the Assessment Group's models resulted in considerably higher ICER estimates for lapatinib plus letrozole compared to trastuzumab plus anastrozole. Since the ICER range quoted in the summary table of the ACD is based on the	Comment noted. The summary of Appraisal Committee's key conclusions section has been amended so that the ICERs from the Assessment Group or the manufacturer are not reported.

Consultee	Comment	Response
	manufacturers' base case estimates (lower end of the range) and the Assessment Group base case estimates (upper end of the ICER range) the ICER range for lapatinib plus an aromatase inhibitor is wider and goes higher than that given for the trastuzumab intervention. This may ultimately affect the perception of the relative clinical and cost-effectiveness of the lapatinib and trastuzumab interventions. Section 4.3.10 of the ACD states: *"The Committee considered that the Assessment Group's estimates were likely to be an overestimate 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 underestimated (section 4.3.8) by the Assessment Group. The Committee discussed the manufacturer's estimate of the ICER. On the basis of previous discussions regarding post-progression survival (section 4.3.9) the Committee concluded that the most plausible ICER would be higher than £74,000 per QALY gained."* Given the comments above regarding the Assessment Group's estimates we suggest that it would be more appropriate in the 'key conclusions' section of the document (page 36) to state the Appraisal Committee's conclusion regarding the ICER for lapatinib rather than the range covered by the Manufacturer and Assessment Group estimates.	
GlaxoSmithKline	**2.2. Factual inaccuracies** **a) Section 4.3.4 page 25** *"The Committee noted that, in TAnDEM, 9 patients had not progressed after 16 months, although in EGF30008 the number was also small (18 patients) and this added to the uncertainty in the estimation of meal survival"* 'meal' should be replaced with 'mean'. **b) 'Summary of Appraisal Committee's key conclusions', 'Uncertainties around and plausibility of assumptions and inputs in the economic model', page 38.** *"The Committee heard from clinical specialists that there is no reason why treatment with lapatinib prior to progression should result in either a shorter or longer duration of post-progression survival."*	Comment noted. Section 4.3.4 in the ACD has been removed from the FAD and so this sentence is no longer in the FAD. Comment noted. Sections 4.3.8 and 4.3.12 of the FAD and the relevant section in the key conclusions table in the FAD have been amended (page 35).

Consultee	Comment	Response
	This statement also applies to trastuzumab refer to section 4.3.13 of the ACD. The suggested revision is as follows: The Committee heard from clinical specialists that there is no reason why treatment with lapatinib or trastuzumab prior to progression should result in either a shorter or longer duration of post-progression survival.	
GlaxoSmithKline	**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** As stated above GSK remains concerned about the modelling approach employed by the Assessment group in this MTA and the impact that this may have on the perceived relative cost-effectiveness of the interventions under consideration. However we recognize that addressing this issue is unlikely to affect the provisional recommendation since the ICER estimates are not within the range normally considered cost-effective by NICE.	Comment noted.
GlaxoSmithKline	**4. 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?** GlaxoSmithKline does not believe that there are any aspects of the recommendation that need particular consideration to ensure that NICE avoid unlawful discrimination.	Comment noted.
GlaxoSmithKline	**5. Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?** GlaxoSmithKline does not believe that there are equality related issues needing special consideration which have not already been highlighted in our submission.	Comment noted.

Consultee	Comment	Response
Roche	**1. Has all the relevant evidence been taken into account?** No. The Committee has not taken into account several pieces of evidence that must be appropriately considered if a sound conclusion on the clinical and cost-effectiveness of trastuzumab is to be reached. This includes the different prognostic status of patients in the TAnDEM and EGF30008 trials, the different modes of action of trastuzumab and lapatinib, and the wealth of data supporting the assumption of increased survival associated with trastuzumab.	Comment noted. Please see responses to each part of this comment below.
Roche	**Point 1: Cross-trial comparisons of progression-free survival experienced in Tandem and EGF30008** In Section 4.3.3. of the ACD it is stated that "The Committee noted that the curves showing the percentages of people alive without progression for the treatment arms were similar to each other between the trials. It 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)." A naïve cross-trial comparison of this kind is subject to clear bias against trastuzumab. The EGF30008 population is a better prognostic group than the TAnDEM population. HER2/hormone receptor co-positive disease is particularly aggressive. The TAnDEM population had a heavier burden of metastatic disease than the EGF30008 population and as a consequence had a poorer prognosis, ie the rates of metastases at a number of different sites are greater in the TAnDEM study than they are in the EGF30008 study for bone (56.5 vs 15.2%), lung (44.0% vs 37.9%) and soft tissue (43.5 vs 30.1%), and the number of lesions per patient is higher in the TAnDEM study (median of 4 with a range up to 14). The median time from diagnosis of metastatic disease in TAnDEM is particularly short at 1.4 months supporting the population having more advanced and aggressive disease. Indeed, the assessment group had already identified differences in the patient populations in EGF30008 and TAnDEM when they concluded that "key differences in the trials led the AG to the conclusion that it would not be appropriate to pool data or make meaningful comparisons, directly or indirectly, across the two completed trials." (page 37, Liverpool Assessment Report). This was their conclusion as a consequence of the fact that the "EGF30008 trial excluded patients in which the	Comment noted. The Committee noted the comments received during consultation on the post-appeal appraisal consultation document. It discussed the difficulties with comparing the trials and was uncertain to what extent the trials could be compared. (see FAD section 4.3.3) Section 4.3.4 in the ACD is no longer in the FAD. Sections 4.3.12 and 4.3.14 of the FAD have been amended accordingly.

Consultee	Comment	Response
	disease was considered by the investigator to be rapidly progressing or life threatening" (page 36, Liverpool Assessment Report). For ease of reference the characteristics of patients in TAnDEM and EGF30008 are reproduced below. (Table not reproduced here) It is important that the Committee appropriately consider these differences and the implications that this has for the assessment of the relative effectiveness of lapatinib and trastuzumab. In the current ACD these differences do not appear to be considered appropriately. Section 4.3.3 of the ACD continues with the statement "Conversely, the Committee noted that the percentages of people alive and progression free for the comparator arms were different, and that this was the explanation for the difference in gain between treatment and comparator between the two trials. The Committee concluded that any apparent benefit in mean progression-free survival with trastuzumab compared with lapatinib was based on the difference between the aromatase inhibitor arms in the two trials." Given the differences in patient population provided in Tables 1 and 2 above, we disagree that the reason for a worse PFS in the AI arm in TAnDEM is due to "underperformance" as suggested in the ACD. There is a clear rationale why we would expect a difference in the AI arms in the two trials and this can be seen in the difference in baseline characteristics between the two trials. Furthermore, the Committee's suggestion that the trastuzumab+AI arm is 'accurate' whilst the AI monotherapy arm is 'underperforming' would suggest the Committee is questioning the validity of the randomisation procedure in the TAnDEM trial. TAnDEM was a high quality, robust study run to regulatory submission standards. In conclusion, if the Committee believe that the anastrozole arm from TAnDEM is not representative of the clinical benefit that would be observed in real-world practice (that it would instead be even better), if they accept that randomisation was accurately performed, then it must also be believed that the trastuzumab+anastrozole arm is also underperforming relative to what would be expected in real-world practice. This issue appears again in Section 4.3.12 of the ACD which states "On the basis of previous discussions regarding the aromatase inhibitor data from the TAnDEM trial (section 4.3.4), the Committee concluded that the estimates of progression-free	

Consultee	Comment	Response
	survival from the manufacturer of trastuzumab and the Assessment Group were likely to underestimate progression-free survival for the aromatase inhibitor group." As noted above, this logic dismisses the difference of patient prognosis between the two RCTs and assumes that randomisation was not correctly performed in the TanDEM trial. If it is accepted that randomisation was performed correctly, it should also be concluded that Roche has underestimated progression-free survival for the trastuzumab+AI group. Finally, in Section 4.3.14 of the ACD it is concluded that "The Committee accepted that the manufacturer's estimate was too low given that people in the aromatase inhibitor group appeared to progress much quicker than would be expected in clinical practice (sections 4.3.4 and 4.3.12)". Following the arguments provided above, if it is assumed that both arms are underperforming in the TanDEM trial, then the incremental QALY gain would actually be larger if these were adjusted to reflect a better-prognostic population.	
Roche	***A comparison of laptinib and trastuzumab – mode of action, half-life and head to head evidence*** While the question of potentially comparable effectiveness between the two HER2 targeted therapies has been unknown since the launch of lapatinib, recent evidence has suggested that it cannot be assumed that lapatinib is equally as efficacious as trastuzumab. These two treatments have different modes of action that translates to different clinical efficacy and different tolerability profiles. Trastuzumab is a recombinant humanised IgG1 monoclonal antibody against the human epidermal growth factor receptor 2 (HER2). It binds with high affinity and specificity to sub-domain IV, a juxta-membrane region of HER2's extracellular domain. Binding of trastuzumab to HER2 inhibits ligand-independent HER2 signalling and prevents the proteolytic cleavage of its extracellular domain, an activation mechanism of HER2. Additionally, trastuzumab is a potent mediator of antibody-dependent cell-mediated cytotoxicity (ADCC).In contrast, lapatinib is an inhibitor of the intracellular tyrosine kinase domains of both EGFR (ErbB1) and of HER2 (ErbB2) receptors which inhibits ErbB-driven tumour cell growth. As a small molecule, lapatinib does not mediate ADCC and has a short half-life and wash out period. In short there is a biological rationale for greater effectiveness with trastuzumab as it has mechanisms of action not available to lapatinib. The KM curve from TAnDEM shows a later PFS gain but the benefit is sustained. In	Comments noted.

Consultee	Comment	Response
	contrast, the KM curve from EGF30008 demonstrates an earlier PFS gain but the benefit is not sustained. (Figure not reproduced here) Furthermore, trastuzumab and lapatinib are not equally effective in the treatment of early breast cancer. Trastuzumab is licensed in both the adjuvant and neoadjuvant settings. Treatment with trastuzumab for one year, following or concurrent with chemotherapy improves disease free and overall survival (Smith et al, 2007; Perez et al, 2011; Slamon et al, 2011). In the NOAH study, the addition of trastuzumab to neoadjuvant chemotherapy resulted in significant improvement in event-free survival (Gianni et al, 2010). Conversely, on August 18th 2011 the lapatinib monotherapy arm of the ALTTO (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation) study was discontinued, because the comparison of this arm with the trastuzumab alone arm crossed the futility boundary, indicating that the lapatinib monotherapy arm was unlikely to meet the pre-specified criteria to demonstrate non-inferiority to trastuzumab alone with respect to disease-free survival (DFS) (ALTTO study, details available from clinicaltrials.gov). Additionally, the authors of the GeparQuinto, GBG 44 study (lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy) concluded that because **pathological complete response rate with chemotherapy and lapatinib was significantly lower than that with chemotherapy and trastuzumab,** lapatinib should not be used as single anti-HER2-treatment in combination with neoadjuvant chemotherapy, outside of clinical trials (Untch et al, 2012). Given these differences in mode of action and efficacy in the early breast cancer setting, we do not agree it is reasonable to conclude that there is no difference in the clinical effectiveness of trastuzumab and lapatinib.	
Roche	**Point 2: Overall survival gain estimates for trastuzumab** In Section 4.3.14 of the ACD, it is stated that “The Committee heard from the Assessment Group that this does appear to be an anomaly but that it is caused by a problem in the data in the control arm of the trial, raising further questions of uncertainty in the data. For the same reason as discussed for lapatinib (section 4.3.9) the Committee concluded that the likely impact on post-progression survival	Comment noted. The Committee discussed comments received during consultation and concluded that there was a considerable lack of clarity around the relationship between progression-free survival and post-progression survival (see FAD section 4.3.12). Section 4.3.14 of the

Consultee	Comment	Response
	with trastuzumab was most likely to be nearer to zero." Firstly, we have not seen any explanation/evidence of this anomaly in the TAnDEM data as suggested by the AG. We believe this is unacceptably vague wording and should be clarified for the purposes of appropriate decision making. Furthermore, the assumption on no impact of trastuzumab post-progression does not take into account the half-life of trastuzumab which is 28-38 days and subsequently the washout period is up to 27 weeks (190 days or 5 elimination half-lives) (Herceptin Summary of Product Characteristics). In contrast, the half-life of lapatinib is 24 hours (Tyverb Summary of Product Characteristics). This is supported by a wealth of evidence across several RCTs for trastuzumab which suggests that OS gains are consistently larger than PFS gain for trastuzumab containing regimens. (Table not reproduced here) However, even if the Committee assumes that there is zero impact of trastuzumab post-progression as stated in Section 4.3.14 of the ACD, this would still translate the observed mean PFS advantage of 8 months from TanDEM into a mean OS advantage of 8 months.	FAD has also been changed.
Roche	**Point 3: End of Life 3-month survival criterion** Section 4.3.19. of the ACD describes the deliberation on the extension of life criterion. "The Committee noted that the estimates of survival gain based on the economic model were higher than 3 months. However, these estimates of overall survival were subject to considerable uncertainty because of limited availability of follow up data." We are unclear precisely what is considered so limited about the availability of follow-up data in TAnDEM. This trial was completed several years ago, and the final data cut-off of April 2008 represents a median follow-up of 3.1 years (and maximum follow-up of 6.2 years). This is considerably longer than most metastatic cancer RCTs reviewed by NICE, given the length of time that has passed in this particular instance between the marketing authorisation in September 2008 and the current assessment of this data by NICE. Section 4.3.19. of the ACD continues by stating that "The Committee considered that the level of uncertainty in the estimates of survival gain was so great that there was insufficient evidence of a survival gain of at least 3 months. The Committee reiterated its view that the most robust evidence of efficacy is provided by a statistical significant survival gain. The Committee concluded the evidence was not	Comment noted. The end of life criteria are applied in exceptional circumstances and are an exception to NICE's usual procedures. The supplementary advice states that robust evidence of a 3 month gain is required, whereas for the purposes of appraisals that fail to meet the end of life conditions, the Committee is at liberty to take a different attitude to uncertainty. In the second post-Appeal Committee meeting, the Committee discussed whether a 3 month survival gain could be inferred from the data provided. It concluded that as trastuzumab did not meet the end of life criterion for life expectancy, it was not necessary to make a decision about the extension to life criterion (see FAD section 4.3.17).

Consultee	Comment	Response
	sufficient or robust to indicate that trastuzumab plus an aromatase inhibitor provided a 3-months survival gain and so it did not fulfil the criteria for life extension." Whilst we do agree that statistical significance is one of the most important measures used in frequentist statistics, we do not agree that it should be considered as the only measure of robustness in NICE appraisals. The 5% significance level represents an arbitrary rule of inference and has been argued by some to be irrelevant to the decisions which clinical and economic evaluations claim to inform (Claxton, 1999). The OS estimates provided when adjusting for cross-over as reported in section 4.1.10 of the ACD may not have been *significant* at a 5% level as the upper bounds of the 95% confidence interval marginally exceeded 1 (OS HR = 0.73, 95% CI 0.51 to 1.04) but it would have been *significant* at a 10% level (90% CI 0.54 to 0.98) had an arbitrary 10% significance level been chosen instead. Furthermore, the lack of statistical significance at the 5% level can largely be attributed to the fact that, like many other trials for end of life treatments, the TAnDEM trial was not powered to show statistically significant difference in overall survival and suffers from extensive cross-over onto the intervention arm in the placebo arm. All the figures presented to the Appraisal Committee over the course of this appraisal have suggested a greater than 3 month gain in overall survival and, in the spirit of the Bayesian approach which the NICE Guide to Methods is based, should be considered despite the lack of statistical significance at the 5% level. (Table not reproduced here). The Committee has previously also referred to the evidence for progression-free survival gain and commented that this appeared convincing, and could be taken as a surrogate measure for overall survival. Whilst it is possible in some situations that PFS may be required as a surrogate for OS, this is not necessarily appropriate when mature randomised control trial OS data are available. Furthermore the Committee focused on the median PFS gain of 2.4 months rather than the mean PFS gain of 8.6 months (undiscounted mean PFS gain from the TAnDEM Kaplan-Meier PFS curves). The mean PFS figure is more appropriate to consider than the median PFS from TAnDEM, given that at the point of data cut-off (April 2008), all patients had progressed and therefore the PFS curve is complete (and requires no extrapolation). There are also previous examples where a new intervention (e.g. pazopanib for	

Consultee	Comment	Response
	renal cell carcinoma TA215) has been accepted under the End of Life criteria without a significant OS benefit. One of the key differences between pazopanib and trastuzumab, though, would be the wealth of evidence spanning several RCTs where trastuzumab has demonstrated again and again a clinically and statistically significant OS benefit. We present below a number of overall survival Kaplan-Meier plots for pivotal metastatic trastuzumab RCTs.	
Roche	**2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** Section 2.4 states "Tumours that overexpress the HER2 protein (HER2+) grow and divide more quickly." Similar to the paragraph 2.3 above which describes the prognosis associated with hormone receptor status, this section should also clarify that overexpression of HER2 is associated with a worse prognosis. We would suggest the following wording adjustment: "Tumours that overexpress the HER2 protein (HER2+) grow and divide more quickly and as a consequence, women with HER2 overexpression generally have a worse prognosis than women who do not have HER2 overexpression."	Comment noted. Section 2.4 of the FAD has been amended.
Roche	Section 3.5 states "The SPC states that the most common adverse events associated with trastuzumab therapy are cardiotoxicity, infusion-related reactions, haematotoxicity (in particular neutropenia) and pulmonary events." These adverse events are associated with trastuzumab when given in combination with chemotherapy and this should be reflected in the above sentence. We would recommend the following amendment to this sentence: "The SPC states that the most common adverse events associated with trastuzumab when given in combination with chemotherapy are cardiotoxicity, infusion-related reactions, haematotoxicity (in particular neutropenia) and pulmonary events."	Comment noted. Section 3.5 of the FAD has been amended.
Roche	Section 3.6. "The recommended dosage of trastuzumab is a loading dose of 4 mg/kg by intravenous infusion, followed by a weekly maintenance dose of 2 mg/kg until disease progression. Alternatively, a loading dose of 8 mg/kg can be given, followed by 3-weekly maintenance doses of 6 mg/kg until disease progression." This language may suggest that the former described schedule is recommended/preferred above the latter described schedule. To correct this, we	Comment noted. Section 3.6 of the FAD has been amended.

Consultee	Comment	Response
	would suggest the following amendment to this section: "The recommended dosage of trastuzumab is either a loading dose of 4 mg/kg by intravenous infusion, followed by a weekly maintenance dose of 2 mg/kg until disease progression or a loading dose of 8 mg/kg by intravenous infusion, followed by 3-weekly maintenance doses of 6 mg/kg until disease progression."	
Roche	Section 4.3.4 states "The Committee considered the differences in progression-free survival between the aromatase inhibitor groups in the trials….. The Committee further noted the protocol amendment to allow people in the aromatase inhibitor alone group in TAnDEM to receive trastuzumab. It considered that this amendment may add additional uncertainty to the validity of the data from the aromatase inhibitor group in this trial, particularly if fitter people left the group earlier than they otherwise might, although no data were available to confirm if this was the case." This is an incorrect flow of thought given that this protocol amended only to allow for cross-over to occur post-progression, which therefore would not impact on PFS results. Please can this be re-considered. Section 4.3.4 also states "….this added to the uncertainty in the estimation of meal survival." Meal should be replaced with mean, assuming this was the Committee's intention however, please see above the clarification which may remove this assumed uncertainty	Comment noted. Section 4.3.4 in the ACD has been removed from the FAD.
Roche	Section 4.3.18 states "The Committee noted that a range of overall survival estimates were presented, from the median survival in the ITT population of 23.9 months, median survival in the centrally confirmed population of 28.6 months and the Assessment Group and manufacturer's estimates of mean survival of 29 and 31 months respectively…The Committee concluded that all the evidence on survival indicated that patients receiving current standard NHS treatment would have an expected survival greater than 24 months." For completeness, these estimates presented here do not include the RPSFT median (the median from the TanDEM trial which attempts to take into account the post-progression trastuzumab received in the AI (placebo) arm) which was 22 months survival.	Comment noted. Section 4.3.16 of the FAD has been amended to include the RPSFT median.
Roche	**3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** No comment.	Comment noted.

Consultee	Comment	Response
Roche	**4. 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?** This population represents untreated metastatic breast cancer patients who are older (e.g. post-menopausal), overexpressing HER2 (e.g. poorer prognosis than their HER2-negative counterparts), and who are not appropriate for chemotherapy (e.g. not eligible for the NICE-approved standard of care of trastuzumab in combination with chemotherapy). We are therefore concerned that this may represent discrimination against a very small population of elderly patients who would otherwise not have access to a proven effective treatment.	Comment noted. Section 4.3.24 of the FAD refers to the issue of discrimination.
Roche	**5. Are there any equality-related issues that need special consideration and are not covered in the appraisal consultation document?** No comment.	Comment noted.
Royal College of Nursing	**Has the relevant evidence has been taken into account?** The evidence considered seems comprehensive.	Comment noted.
Royal College of Nursing	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We would ask that the summaries of the clinical and cost effectiveness of this appraisal should be aligned to the clinical pathway followed by patients with metastatic hormone-receptor-positive breast cancer that over-expresses HER2**.** The preliminary views on resource impact and implications should be in line with established standard clinical practice.	Comment noted. The summaries of clinical and cost effectiveness are summaries of the evidence included in the manufacturers' submission, so they may not be fully aligned to the clinical pathway.
Royal College of Nursing	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** Nurses working in this area have reviewed the recommendations of the Appraisal Committee and do not have any other comments to make. The RCN would welcome guidance to the NHS on the use of this health technology.	Comment noted.
Royal College of Nursing	**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?** None that we are aware of at this stage.	Comment noted.
Royal College of Nursing	**Are there any equality-related issues that need special consideration that are not covered in the appraisal consultation document?**	Comment noted.

Consultee	Comment	Response
	We are not aware of any specific issue at this stage. We would however, ask that any guidance issued should show that an analysis of equality impact has been considered and that the guidance demonstrates an understanding of issues relating to all the protected characteristics where appropriate.	
Breakthrough Breast Cancer	Breakthrough Breast Cancer is dedicated to improving and saving lives through breast cancer prevention, early diagnosis, more targeted treatments and better services for everyone affected by breast cancer. This submission reflects the views of Breakthrough, based on our experience of working with people with personal experience of, or who are concerned about, breast cancer. We regularly consult with members of our Campaigns and Advocacy Network (Breakthrough CAN) for their views on a range of breast cancer issues. Breakthrough CAN brings together over 1,800 individuals, regional groups and national organisations across the UK to take action locally on our national campaigns to secure important improvements to breast cancer research, treatments and services. Through supporting and training members, Breakthrough CAN aims to increase the influence of breast cancer advocates in decisions regarding breast cancer issues. Breakthrough welcomes the opportunity to comment on this appraisal consultation document. We are disappointed the Appraisal Committee is unable to recommend lapatinib or trastuzumab in combination with an AI for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2.	Comments noted.
Breakthrough Breast Cancer	**Has all the relevant evidence been taken into account?** There is no cure for metastatic breast cancer and treatment options are used to alleviate symptoms, delay progression or improve survival. For this patient group maintaining quality of life for as long as possible is currently the best outcome. Some women may live full lives for some time and treatments that can help them to do this are welcomed. It is therefore essential more treatment options are made available to this patient group. Treatment with trastuzumab or lapatinib plus an AI has been shown to be more effective than treatment with an AI alone. Findings from both TAnDEM and EGF30008 trials found that although no statistically significant gains were made in	Comments noted. The Committee concluded that neither lapatinib nor trastuzumab would be a cost-effective use of NHS resources when combined with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2.

Consultee	Comment	Response
	overall survival when trastuzumab or lapatinib were added to an AI, the gains in progression free survival were significant. Progression-free survival is something that patients with metastatic breast cancer say is very important to them. Delayed time to disease progression, if associated with few severe side effects of treatment, allows patients with metastatic breast cancer to continue with some aspects of their normal daily life and delays the associated debilitating symptoms and emotional distress this progression may bring. It may also allow the patient to be able to continue to carry out normal daily activities such as caring for their families or continuing to work or simply enjoying spending quality time with their loved ones. For patients with metastatic breast cancer the importance of this should not be underestimated. Lapatinib plus an aromatase inhibitor has the added advantage of being an oral treatment. As a first line treatment for metastatic breast cancer this is a very attractive option as it would be easier for patients to carry out their lives in as normal a way as possible and reduce the time spent visiting hospital. Administration by tablet form also reduces NHS costs of treatment provision as well as patient costs associated with attending hospital such as parking, travel, time off work and child care.	
Breakthrough Breast Cancer	**Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?** We are disappointed the Appraisal Committee is unable to recommend lapatinib or trastuzumab in combination with an AI for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. As a patient organisation, Breakthrough would like to emphasise how crucial it is for this patient group to have treatment options, especially ones that can improve quality of life and allow as little disruption to normal life as possible. The TAnDEM and EGF30008 clinical trials which looked at the efficacy of combining these hormone and biological therapies showed clinical benefit and statistically significant gains in progression free survival upon combination. However, Breakthrough acknowledges that combining AIs with lapatinib or trastuzumab is an expensive treatment.	Comment noted.
Breakthrough Breast Cancer	**Are the provisional recommendations sound and a suitable basis for guidance to the NHS?** It is vital that the appraisal process is seen by all stakeholders to be fair and rigorous	Comment noted.

Consultee	Comment	Response
	and that all conclusions are clearly stated. Therefore, we welcomed the fact that the appeal regarding the original ACD was successful and that as a result the end of life criteria with relation to trastuzumab plus an aromatase inhibitor were revisited, even though this did not change the overall decision not to approve this treatment.	
Breakthrough Breast Cancer	**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?** None of which we are aware	Comment noted.
NCRI/RCP/RCR/ACP/JCCO	I write on behalf of the NCRI/RCP/RCR/ACP/JCCO who collaborate when responding to NICE oncological consultations. We are grateful for the opportunity to comment on the above ACD and would like to make the following comments. The conclusions of the ACD seem to be reasonable in so far as they go but will be disappointing to patients with metastatic breast cancer and to clinicians who treat them. The most fundamental issue in the appraisal is that no comparison was performed in the cost-effectiveness of anti-HER2 therapy combined with an aromatase inhibitor with trastuzumab in combination with chemotherapy or even with trastuzumab monotherapy. Both of these therapeutic options have previously been recommended by NICE for women with HER2 positive metastatic breast cancer (although in rather restricted circumstances for trastuzumab monotherapy). In current clinical practise these options are the only way in which anti-HER2 therapy can be delivered to this patient group. For the population considered in the appraisal, if patients wish to avoid chemotherapy or clinicians are reluctant to give chemotherapy then the options for the majority are either initial treatment with an aromatase inhibitor as monotherapy or reluctant acceptance of chemotherapy and trastuzumab. Those who are treated initially with endocrine therapy, which the randomised evidence considered by the NICE committee clearly shows is inferior to AI and anti-HER2 combination therapy, will be forced into a decision about chemotherapy as a means to obtain anti-HER2 therapy at the point of failure of endocrine therapy. There is no trial data comparing endocrine therapy in combination with anti-HER2 therapy, either alone or in combination with chemotherapy which makes a comparison of efficacy very difficult but this is the	Comments noted. The scope of the appraisal highlighted that trastuzumab and lapatinib should be compared with each other and should also be compared with aromatase inhibitors. Chemotherapy was not listed as a comparator in the scope.

Consultee	Comment	Response
	real world decision facing patients and clinicians. Availability of anti-HER2 therapy in combination with an AI is a suitable treatment for those few patients for whom chemotherapy is not an option. The recent dramatic price fall in the cost of anastrozole and letrozole as these drugs have come off patent will affect the economic assessments performed for the Committee although probably not to a significant degree. They would however significantly affect any comparison between antiHER2 therapy and AI's with chemotherapy and trastuzumab. The Committee commented that the TAnDEM and EGF100151 trials showed a very uncertain overall survival gain. The trial data however is clearly skewed by crossover of patients in the TAnDEM trial to trastuzumab post-progression. This is also likely but undocumented for those enrolled in EGF100151.	

Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Healthcare Improvement Scotland	First, what looks like an error: section 4.2.21: gain of 316 days pre-progression survival with lapatinib treatment I think should be gain of 316 days pre-progression survival with trastuzumab treatment	Comment noted. Section 4.2.21 of the FAD has been amended.
Healthcare Improvement Scotland	Some comments - though I don't know how sensitive the conclusions are to the following data/assumptions! The various models (including that done by the independent group) all use slightly different utility values for progression-free and post-progression states. given that utility values are a very inexact science this is, in my personal view, giving greater weight to small differences in utilities too far. Similarly for the disutilities - we ascribe a greater value (1.2) to alopecia than to diarrhoea - Section 4.3.3 - the committee's view on the indirect comparison between the two main studies. Given that both are modest sized trials, the confidence intervals of the data are wide- so I don't see that any clinical statistician would allow such a difference to be drawn. Furthermore, in the one trial that compares the two aromatase inhibitors there was no real difference (letrozole was only marginally better, and the trial was not conduced in the HER2+ population).Therefore I don't think the data support the committee's view;	Comments noted. The Committee noted the comments received during consultation on the post-appeal appraisal consultation document. It discussed the difficulties with comparing the trials and was uncertain to what extent the trials could be compared (see FAD section 4.3.3).

Nominating organisation	Comment	Response
	The Committee concluded that any apparent benefit in mean progression-free survival with trastuzumab compared with lapatinib was based on the difference between the aromatase inhibitor arms in the two trials. In reality, it would be better to say that the apparent differences between the trials may reflect different patient populations as well as the natural imprecision in modest-sized clinical trials, and don't in my view offer any robust evidence in differences in efficacy between any of the agents (either for or against a real difference)	
Healthcare Improvement Scotland	4.3.5 - I would really value the view of an independent statistician with expertise in cancer meta-analysis here. Every trial has different populations - the question is whether the differences are such that they invalidate a meta-analysis which has the advantage of increasing the precision of the estimate of the effect - after all, clinical trials only provide an ESTIMATE of the effect, they rarely produce the precise figure that would be seen in a full population! Sections 4.3.4, 4.3.12 & 4.3.14 highlight concerns as to which trials is the better estimate of the AI treated alone population in "real life": it is not clear to me how they conclude that EGF30008 is the better estimate, other than "clinical impression". So, again, why not meta-analyse the two? Indeed, since this is an MTA asking the question as to whether it is cost-effective to add an anti-HER2 therapy to an aromatase inhibitor, it would seem more logical to me to start with a meta-analysis and then see what the data show….and this might allow a more precise estimate of the difference, if there is any, in the overall survival !	Comment noted. Section 1.1.1 of the Assessment Report explains the Assessment Groups' reasons for not performing a meta-analysis.
Healthcare Improvement Scotland	finally - the whole question of the survival gain - it is extremely unclear what survival gain there would be as the post-progression treatments are not specified, nor protocol mandated (other than in Tandem allowing post-progression cross-over to trastuzumab): in particular patients may well have gone on to get chemo+trastuzumab in any of the4 arms of the trial. In most cases, the post-progression survivals are ~2 years, which suggests that the patients have had several more treatments, and I would suggest that models that depend on the estimated overall survivals are give less weight than those that use the primary PFS data! I would agree however that the data in the trials suggest that the 2 year "end-of-life" criteria are probably not met!	Comment noted.
Healthcare Improvement Scotland	4.3.23 - I don't understand. if either of these indications was approved, the likely population of patients is the same - why is it relevant that there are other patients for whom trastuzumab licensed? Or is that just a "NICE rule" with no real clinical relevance to the population being looked at in the MTA?	Comment noted. The small population criterion for end of life treatments specifies that the cumulative population for all licensed indications of a technology should be considered.

Nominating organisation	Comment	Response
Healthcare Improvement Scotland	Finally the statement The Committee concluded that neither lapatinib nor trastuzumab would be a cost-effective use of NHS resources when combined with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2. should it not read The Committee concluded that neither lapatinib nor trastuzumab would be a cost-effective use of NHS resources when combined with an aromatase inhibitor for the first-line treatment of metastatic hormone-receptor-positive breast cancer that overexpresses HER2 as compared to the use of an aromatase inhibitor alone. since that is the question that has been addressed - as the committee acknowledges, the question as to whether it would be cost-effective compared to chemotherapy+trastuzumab, which is clinically sometimes the more relevant comparison, cannot be addressed from the data in the three trials considered?	Comment noted. Section 4.3.23 of the FAD has been amended to include the suggested text.

Comments received from commentators

Commentator	Comment	Response
Healthcare 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, I think relevant evidence have been taken into consideration.	Comment noted.
Healthcare Improvement Scotland	**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*?** The current clinical practice is to offer combination chemotherapy and Herceptin for this group of patients, however, this is the case as the Herceptin / AI combination is not available within NHS. I think you will find that most clinicians will consider Herceptin / AI combination their first choice if this is made available to them. The conclusion states that Clinicians choice is to give chemo / Herceptin is not a valid one in my view. It is very unlikely that an overall survival will be noticed in this group of patient and PFS end point in my view is justified**.**	Comment noted.

Commentator	Comment	Response
Healthcare Improvement Scotland	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?*** Generally sound and reasonable recommendation taking the cost factor into account.	Comment noted.
Healthcare Improvement Scotland	**4. Are the patient pathways and treatment options described in the assessment applicable to NHSScotland? If not, how do they differ in Scotland?** Yes. Very similar.	Comment noted.
Healthcare Improvement 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.*** I do not expect a change in patient pathways. The expected number for potentially eligible patients in Scotland is in the region 20-40 patients / year based on a figure of 4000 new cases / year and that 15% are HER2 + of whom 50% are ER+. **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.	Comment noted.

No comments received from members of the public