[redacted]

19 January 2011

RE: ACD on the utilization of lapatinib and trastuzumab in combination with an aromatase inhibitor for the first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2

Dear [redacted]

Thank you for giving us the opportunity to comment upon the ACD for the above multiple technology appraisal. Our comments are summarized under the four standard headings below.

If any further clarification or analyses are required in order to aid the Committee's deliberations we would be more than happy to provide them.

Yours Sincerely,

[redacted]

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I. Has all of the relevant evidence been taken into account?

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 identified some concerns with the AG model.

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.

Table 3. Comparison of the lifetime incremental costs of anastrozole +/- trastuzumab from the original base case results presented by Roche and the AG

	Roche Original Submission Model			Assessment Group Model		
Costs	**TRA + ANA**	**ANA**	**Inc**	**TRA + ANA**	**ANA**	**Inc**
Total Drug Costs	**£24,774**	**£445**	**£24,330**	**£31,272**	**£497**	**£30,775**
Total Administration Costs	**£4,301**	**£518**	**£3,783**	**£4,978**	**£52**	**£4,927**
PFS Supportive Care	£2,761	£1,211	£1,550	£2,381	£963	£1,418
PD Supportive Care	£19,481	£17,741	£1,740	£9,168	£10,231	-£1,063
End of Life Costs	£3,375	£3,409	-£34	£1,696	£1,647	£49
Adverse Events Costs	£56	£17	£39	£92	£0	£92
Total Other Costs				£1,898	£602	£1,297
Total Costs	**£54,749**	**£23,341**	**£31,408**	**£51,487**	**£13,992**	**£37,495**

Table 4. Comparison of the lifetime incremental effects of anastrozole +/- trastuzumab from the original base case results presented by Roche and the AG

	Roche Original Submission Model			Assessment Group Model		
Effectiveness	**TRA + ANA**	**ANA**	**Inc**	**TRA + ANA**	**ANA**	**Inc**
PFS Life Years	1.19	0.52	0.67	1.30	0.53	0.77
PD Life Years	2.22	2.02	0.20	1.52	1.69	-0.17
Total Life Years	**3.41**	**2.55**	**0.87**	**2.82**	**2.22**	**0.60**
PFS QALYs	0.87	0.38	0.49	1.00	0.40	0.60
PD QALYs	1.00	0.91	0.09	0.76	0.84	-0.08
Total QALYs	**1.87**	**1.29**	**0.58**	**1.76**	**1.24**	**0.51**

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).

2. Estimation of Overall Survival

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.

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 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:

1. 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.
2. 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 1. Base case costs for trastuzumab in combination with anastrozole versus anastrozole monotherapy

Costs	TRA+ANA	ANA	Inc
Cost of Trastuzumab	£23,677	£0	£23,677
Cost of Anastrozole	£1,097	£445	£652
Total Drug Costs	**£24,774**	**£445**	**£24,330**
Cost of administering Trastuzumab	£3,024	£0	£3,024
Cost of administering Anastrozole	£1,277	£518	£759
Total Administration Costs	**£4,301**	**£518**	**£3,783**
Cost of PFS Supportive Care	£2,761	£1,211	£1,550
Cost of PD Supportive Care	£19,481	£17,741	£1,740
End of Life Costs	£3,375	£3,409	-£34
Adverse Events Costs	£56	£17	£39
Total Other Costs	£25,673	£22,378	£3,295
Total Costs	**£54,749**	**£23,341**	**£31,408**

Table 2. Updated base case outcomes for trastuzumab in combination with anastrozole versus anastrozole monotherapy

Effectiveness	TRA+ANA	ANA	Inc
PFS Life Years	1.19	0.52	0.67
PD Life Years	2.22	2.02	0.20
Total Life Years	**3.41**	**2.55**	**0.87**
PFS QALYs	0.92	0.40	0.52
PD QALYs	1.10	1.00	0.10
Total QALYs	**2.02**	**1.40**	**0.62**

This update results in the following cost-effectiveness estimates:

Cost per Life Year gained = £36,174

Cost per QALY gained = £50,975

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.

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 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.

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.

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 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.

II. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

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).*"

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.

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.

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)).

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.

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.

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.

III. Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

No. Roche believe that trastuzumab in this setting is appropriate for consideration under NICE’s End of Life criteria (see section 1.3) and that the most appropriate cost-effectiveness estimate for trastuzumab is that presented by Roche is section 1.2 of **£50,975 per QALY gained** (and not the estimates presented by the AG (see section 1.1).

IV. 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.

References

Bagust, A et al. Erlotinib monotherapy for the maintenance treatment of non-small cell lung cancer after previous platinum containing chemotherapy: ADDENDUM. Liverpool Reviews and Implmentation Group. September 2010.

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Robins JM, Tsiatis AA. - Correcting for non-compliance in randomized trials using rank preserving structural failure time models. Communications in Statistics Theory 1991; 20(8), 2609-2631

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Weisgerber-Kriegl U, Cirrincione A, and McNiven P. Estimation of the epidemiological effect of trastuzumab over 10 years in five European countries. 44th ASCO Annual Meeting, Chicago, Illinois, USA, 30 May-3 June 2008.