[redacted]

Roche

Tuesday 4th November 2008

Bijal.Chandarana
Technology Appraisal Project Manager
National Institute for Health and Clinical Excellence
MidCity Place
71 High Holborn
LONDON
WC1V 6NA

BY E-MAIL

Dear Bijal,

SINGLE TECHNOLOGY APPRAISAL –
Lapatinib for breast cancer (for use in women with previously treated advanced or metastatic breast cancer)

Thank you for sending us the second Appraisal Consultation Document (ACD) for the above technology appraisal. Please find below comments from Roche presented under the three standard headings.

1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT

a) The ACD does not provide the latest hazard ratio (HR) for time to progression (TTP) of 0.72 (Lapatinib SmPC, June 2008) from the registration trial of lapatinib in combination with capecitabine versus capecitabine monotherapy. (section 3.20)

Section 3.3 of the ACD states that: "***The results reported here all relate to the analysis done using data for the April 2006 cut-off date unless otherwise stated***"

The original planned interim analysis of the pivotal lapatinib trial EGF100151 took place after a data lock on 15th November 2005. The interim analysis, after 114 disease progression events, demonstrated a 4 month improvement in median TTP (4.4 months with C vs 8.4 months with LC, HR 0.49; P<0.001; Geyer et al NEJM 2006).

[redacted]

An updated analysis which included all 399 patients who entered the trial to April 2006 was presented by Prof. Cameron during the ASCO 2007 meeting (Abstract 1035) and subsequently published in *Breast Cancer Res Treat* in January 2008 (submitted and accepted 21 December 2007). This analysis which took place after 184 TTP events, showed the absolute benefit in median TTP had changed from 4 months to 2 months (4.3 (C) to 6.2 (LC) months, HR 0.57; P<0.001; Cameron et al *Breast Cancer Res Treat* 2008)

This updated analysis of the pivotal lapatinib trial, EGF100151, has been in the public domain since presentation at ASCO, June 2007 and appears to have been omitted from the previous submissions made by the manufacturer (original submission [17 April 2007] and from the response to the first ACD [28 July 2008]) and is therefore not included in the current economic model submitted as an addendum.

The updated economic analysis of lapatinib includes the latest TTP and OS data for the trial of trastuzumab and capecitabine (GBG-26) which was first reported at ASCO in June 2008. Updated assumptions about trastuzumab administration based on data from the GBG-26 study were also included in the lapatinib ACD.

In summary, there appears to be a mixture of old and new data contained within the updated economic model and therefore we provide the latest available data reported from analyses of the pivotal lapatinib trial EGF100151 and the trastuzumab study GBG-26 in Table 1 below.

Table 1: Comparison of hazard ratios and incremental benefit in TTP based on GBG-26 and EGF100151 studies.

	Interim analysis of lapatinib + capecitabine as used by manufacturer in submission (Geyer et al 2006)		Updated analysis as reported at ASCO 2007 and detailed in lapatinib SmPC (June 2008)		Trastuzumab + capecitabine randomised controlled trial (GBG-26)
	IRC	INV	IRC	INV	
Incremental TTP **months (wks)**	**4.0 (17.1)** (p<0.001)	**1.6 (6.9)** (p=0.002)	**1.9 (8.1)*** p<0.001	**1.3 (5.6)**** p=0.008	**2.6 (11.1)** (p two-sided p=0.034; one-sided p=0.017)
HR (TTP)	**0.49** (95% CI, 0.34, 0.71)	**0.59** (95% CI, 0.42, 0.84)	**0.57*** (95% CI 0.43, 0.77)	**0.72**** (95% CI 0.56, 0.92)	**0.69** (95% CI 0.49, 0.97)[#]
Incremental OS **months (wks)**	**NR** p=0.72		**0.3 (1.3)*** (P=0.177) **1.9 (8.1)***** p=0.3		**5.1 (21.9)** (two-sided p=0.26; one-sided p=0.13)
HR (OS)	**0.92** (95% CI, 0.58 to 1.46)		**0.78*** (95% CI 0.55, 1.12) **0.90***** (95% CI 0.71, 1.12)		**0.76** (95% CI 0.47, 1.22)[#]

IRC, Independent Review Committee assessment; INV, Investigator assessment; NR, Not Reported

[#]Derived by Roche from published GBG-26 p-values
*Presented in June 2007 analysis (ASCO 2007) and published by Cameron et al *Breast Cancer Res Treat* Jan 2008
**lapatinib SmPC June 2008
***lapatinib SmPC OS analysis incorporating patients from the registration trial who crossed over from capecitabine monotherapy to receive capecitabine plus lapatinib

b) Decrease in hazard ratio of the overall survival results published in the lapatinib SmPC

In section 3.12 of the ACD, the updated LC overall survival data (lapatinib SmPC June 2008) are discussed and the message conveyed is that the OS results have improved in the latest cut-off of the data. Although this is correct in terms of the absolute improvement in weeks, these results show that the updated incremental benefit (HR=0.9; 95% CI 0.71, 1.12) for the LC arm has also decreased since the previous analysis.

c) Previous comments in Roche's response to the first ACD regarding the comparison of hazard ratios from GBG-26 and EGF 100151 have not been taken into consideration in the second ACD

In the round of consultation on the first ACD, Roche also drew to the Appraisal Committee's attention that a more recent analysis of the data for time-to-progression (TTP) from the lapatinib registration trial had been published (Cameron et al 2008). This new information was not included in the revised base-case economic model and was therefore not used in the ERG's and the DSU's analyses. The September 2007 follow-up illustrates that the treatment effect of LC compared to capecitabine monotherapy is not as large as that demonstrated by the 2006 follow-up data utilised in the cost-effectiveness calculations for TTP (see Table 1). This is an extremely important considering the large effect this has on the ICER and therefore so should be taken into account by the Appraisal Committee.

d) Trastuzumab administration frequency and dosing appear to be incorrect

Since the last ACD consultation, the licence of trastuzumab has been amended to include both weekly and three weekly administration for patients with metastatic breast cancer. The SmPC has been changed accordingly and the September 2008 version states the following:

> "**MBC 3-weekly schedule:**
>
> Initial loading dose of 8 mg/kg body weight, followed by 6 mg/kg body weight 3 weeks later and then 6 mg/kg repeated at 3-weekly intervals administered as infusions over approximately 90 minutes."

The licence now reflects clinical practice. Two market research studies commissioned by Roche indicate that trastuzumab is now overwhelmingly given as a 3-weekly regimen in the treatment of MBC.

<u>Double Helix Development study</u>

DHD is an independent market research agency and was commissioned to conduct a market research study which was fielded in May - June 2008. One of the objectives of the study was to assess whether trastuzumab is given as either a weekly or a 3-weekly regimen in EBC and MBC. In order to meet Roche's research objectives, Double Helix Development designed a Patient Case Record (PCR) approach. A sample of oncologists (n=85) completed PCR forms for the last three HER2-positive MBC

patients seen who were currently receiving anti-cancer drug treatment for MBC. The breakdown of the respondent sample can be found in Appendix 1.

Of the respondents, 70% were Consultants and 30% were Specialist Registrars. All had been practising for between 4 and 30 years and were responsible for treatment decisions for HER2-positive breast cancer patients. The sample was spread across UK cancer networks. The breakdown of the cancer networks included in this research can be found in Appendix 1.

The main outcome of the study was that trastuzumab is given as a 3-weekly regimen in 96% of patients.

Genactis study

This market research was conducted in Q4 2007 by Genactis and its main objective was to gain an in-depth understanding of the MBC market and treatment patterns.

The study is descriptive market research using a multiple cross-sectional design. Data collection was achieved by sending Electronic Case Assessment Forms (eCAFs) to physicians. Physicians of 15 prospective patient cases of MBC, commencing a line of treatment, were asked to complete an eCAF and return it to Genactis for analysis. Although this was multicentre and multinational study, the UK was represented by 74 respondents who completed 1110 forms. A total of 1064 forms were collected and analysed. 207 eCAFs included treatment with trastuzumab in the MBC setting. Out of all the 207 patients treated with trastuzumab only 8% were given the weekly regimen, 92% of the patients received the 3-weekly treatment regimen.

Both market research studies demonstrate that trastuzumab is given as a 3-weekly regimen in 92% to 96% of all MBC patients treated.

Although the base-case scenario in the cost-effectiveness analysis has been revised, it still does not reflect treatment patterns observed in UK as demonstrated by the above data.

2 WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE

a) Key elements of the patient access programme are unclear and there is insufficient detail to enable an accurate assessment of clinical effectiveness (sections 3.17, 4.14)

Having reviewed the information on the '*Patient Access Programme*' proposed by GSK, Roche believes that the scheme lacks to a certain degree the transparency required to undertake a thorough evaluation. The main concerns are focussed around the timing of assessments and continuation/discontinuation criteria and how these affect the cost-effectiveness of the scheme.

Although the manufacturer states, “clear criteria will be defined for entry into the programme, as well as continuation and stopping criteria” these are presently unclear in the ACD and therefore Roche believes that further details are required.

Continuation/discontinuation criteria

Roche is concerned that the criteria are very subjective and not as rigid as they could be which may result in subjective decision making and hence regional differences in treatment practice.

Currently the continuation criteria are clinical benefit characterised by the reduction in size or disappearance of existing lesion (whether measurable or not), stable disease and/or improvement of other response criteria including symptom improvement. This may mean that patients could continue treatment because of perceived symptomatic benefit even though in some case this may be a placebo effect.

The criteria may result in inappropriate treatment of patients on lapatinib and capecitabine. An accurate assessment of patients and stringent criteria for stopping or continuing treatment will determine the treatment duration which influences the cost of lapatinib to the NHS, particularly if more patients than expected continue treatment on lapatinib and capecitabine.

Economic evaluation critique

The scheme itself and how it integrates with the manufacturer’s base-case cost-effectiveness analysis has been inadequately presented for consultation.

The main characteristic of the scheme is that a certain percentage of the eligible population will drop-out by the 12th week of treatment. It is unclear if this drop-out/discontinuation rate is the same as the one used in the base-case analysis. If the rate has been assumed to be greater in the scheme than in the base-case model, it would have a direct impact on the cost-effectiveness of the lapatinib treatment as more patients are assumed to stop treatment in the scheme than observed in the trial. The scheme seems to preserve the QALYs gained from the trial data while more patients are assumed to drop-out based on the clinical criteria.

Finally, we also note that the NHS has to initially pay for the treatment for the first 12 weeks that are part of this scheme and that they have to claim back the costs from the manufacturer. As is evident from the manufacturer’s submission it is possible that the claim for reimbursement of costs may be refused if they deem that inclusion criteria have not been met and therefore may result in a unexpected cost to the NHS.

b) The ACD does not provide an accurate summary and representation regarding the clinical significance of trastuzumab beyond progression (section 4.4)

The Appraisal Committee questioned the clinical significance of continuing trastuzumab beyond progression in patients with metastatic disease. Roche would like to draw the Committee’s attention to a randomised clinical trial, GBG-26 (von Minckwitz ASCO 2008) and a single arm prospective trial (Bartsch JCO 2007) which all provide consistent results demonstrating that continuation of trastuzumab beyond progression

(in combination with chemotherapy) extends survival compared with stopping trastuzumab on progression.

The comment made by the DSU in the ACD that the HR for TTP derived from the GBG-26 trial was associated with methodological limitations because randomisation was not maintained is inaccurate; randomisation was maintained, however, the trial was closed early on the recommendation of the Independent Data Monitoring Committee (IDMC).

GBG-26 Study design

The GBG-26 study is a randomised phase III trial, endorsed by the Breast International Group (BIG 3-05; Appendix 2). The results were presented by von Minckwitz et al at ASCO 2008 (Abstract 1025).

Patients who progressed on trastuzumab-based first-line therapy (plus taxane or non-taxane chemotherapy) or trastuzumab monotherapy were randomised to either continue trastuzumab in combination with capecitabine (TC) or stop trastuzumab treatment and receive capecitabine monotherapy (C). The trial planned to recruit 241 patients per arm but closed early on the advice of the IDMC in May 2007, after recruitment of 78 patients per arm. There were two main reasons:

- FDA registration of lapatinib plus capecitabine for trastuzumab progressors. Although GBG-26 was a European study it was believed the EU license for lapatinib in this setting would be granted imminently

- Slow accrual due to unwillingness of HER2-positive patients to stop trastuzumab and therefore enter the capecitabine monotherapy arm.

Results of GBG-26 demonstrated a statistically significant 3 month improvement in TTP for continuing trastuzumab beyond progression versus stopping treatment

The study was originally designed with 80% power to detect a 27.5% improvement in TTP from 4 to 5.1 months for continuing trastuzumab beyond progression. The trial recruited 78 patients per arm and those who continued trastuzumab beyond progression demonstrated a 46% improvement in median TTP from 5.6 (C) to 8.2 (TC) months (HR=0.69: 2-sided p=0.034; 1-sided p=0.015) and 5 month (25%) improvement in OS (from 20.4 to 25.5 months, HR 0.76; P value: 2-sided p=0.26; 1-sided p=0.13) versus patients who stopped trastuzumab on progression.

It emerged during the analysis of GBG-26, that the advantage of continuing trastuzumab beyond progression exceeded the predicted magnitude of benefit such that the number of patients recruited clearly demonstrated a statistically significant and clinically relevant advantage when trastuzumab was continued beyond progression.

c) Potentially misleading conclusions drawn by the manufacturer through extrapolation of the GBG-26 survival data

Roche and GSK presented the data from the GBG-26 clinical trial in the first round of consultation for the use of lapatinib in the treatment of advanced or metastatic breast cancer. The GBG-26 trial results have demonstrated that trastuzumab is effective in the treatment-beyond-progression for second line HER2-positive patients.

Although the results and hazard ratios (shown in table 1 & 2) from this clinical trial have been presented at a peer reviewed conference (ASCO 2008), the manufacturer (GSK) has performed a reanalysis of the GBG-26 survival curves using a method that has resulted in what we consider to be a poor fit of the clinical data. The resulting assumptions have formed the basis of claims of dominance of lapatinib-capecitabine (LC) against trastuzumab-capecitabine (TC) combination therapy.

The reanalysis of the GBG-26 data are presented in Appendix 4 of GSK 's ACD response. The bias of the reanalysis can be clearly observed in Figure 5 (p 35; "*Figure 5. Kaplan-Meier and PH Weibull estimated TTP from GBG 26 /BIG 3-05*") of the document. The model employed by GSK has resulted in a poor fit of the PFS survival data and has underestimated the benefit gained by TC compared to C monotherapy by overestimating the C monotherapy extrapolated curve. The assumption that TC vs C curves have the same shape has produced extrapolated curves that clearly show that the assumption of same shape is not optimal. Relaxing the assumption of the shape would have given parameter estimates that fit the two curves better and would have resulted in a lower HR for the TC arm.

d) The manufacturer's indirect comparison is inconclusive and therefore claims of dominance are highly uncertain

In comparison the trastuzumab arm within the GBG-26 trial demonstrated a median TTP of 8.2 months and an incremental 5.1 months overall survival with a HR=0.76 (two-sided p=0.26; one-sided p>0.05). The latest results from both trials have been placed side-by-side below in Table 2.

Table 2: Comparison of hazard ratios from GBG-26 and EGF100151 studies.

	Trastuzumab + capecitabine randomised controlled trial (GBG-26)	Updated analysis as reported at ASCO 2007 and detailed in lapatinib SmPC (June 2008)
HR (TTP)	**0.69** (95% CI 0.49, 0.97)*	**0.72** (95% CI 0.56, 0.92)
HR (OS)	**0.76** (95% CI 0.47, 1.22)*	**0.90** (95% CI 0.71, 1.12)

*Derived by Roche from GBG-26 p-values

An informal indirect comparison of the two combination therapies against capecitabine monotherapy using the published TTP hazard ratios from both studies, would suggest that patients in the trastuzumab containing therapy stay in the TTP state (HR_{TC}: 0.69 vs HR_{LC}: 0.72) longer than those receiving the lapatinib combination therapy. Both treatments have not shown a significant improvement in overall survival therefore the trastuzumab containing regimen would generate an additional benefit compared to the

benefit generated by the lapatinib therapy. Based on this clinical evidence, Roche believes that GSK's claims that lapatinib dominates the trastuzumab-capecitabine therapy have no basis.

This becomes apparent in the PSA performed by GSK. Figure 7 shows the deterministic value of the ICER, the PSA results and density cloud (appendix 5; A5.2.4). The results clearly show that the LC is about 50% of the time more effective than TC. 50% of the time LC is less effective. Given the deterministic value and the density cloud around this value, the results derived by the base-case model do not support GSK's claim that LC dominates TC. The claims are largely speculative and the two regimens are at best equal in terms of efficacy. The same can be said for the comparisons made between TC and T+vinorelbine (PSA results: appendix 5; A5.2.3, Figure 5) and the comparison between TC and T monotherapy (PSA results: appendix 5; A5.2.5, Figure 9).

Besides the uncertainty surrounding the results, EGF100151 and GBG-26 are not directly comparable as the patient population recruited in the two studies is distinctively different. Therefore the two trials should not form the basis of an indirect comparison.

Based on the above review of the submitted evidence and analysis undertaken, Roche believe that the trastuzumab containing therapies are not less effective and therefore cannot be dominated by lapatinib-capecitabine combination therapy.

3 WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS

Roche would request that the above points are taken into account in the further deliberations of the Committee going forwards.

Please do not hesitate to contact me if you require any further clarification or explanation of our feedback.

Yours sincerely.

Reference

1. Tyverb Summary of Product Characteristics. Date of preparation: 10th June 2008. www.medicines.org.uk

2. Cameron D et al. Lapatinib (L) plus capecitabine (C) in HER2+ advanced breast cancer (ABC): updated efficacy and biomarker analysis. American Society of Clinical Oncology 2007: Presentation. www.asco.org

3. Cameron D et al. A phase III randomized comparison of lapatinib plus capecitabine versus capecitabine alone in women with advanced breast cancer that has progressed on trastuzumab: updated efficacy and biomarker analyses. Breast Cancer Res Treat 2008. Published online: 11th January 2008

4. Geyer CE et al. Lapatinib plus capecitabine for HER2-positive advanced breast cancer. N Engl J Med 2006; 355: 2733-43

5. Von Minckwitz G et al. Capecitabine vs. capecitabine + trastuzumab in patients with HER-2 positive metastatic breast cancer progressing during trastuzumab treatment – the TBP phase III study (GBG 26 / BIG 3-05). 44th American Society of Clinical Oncology annual meeting 2008; Poster. www.asco.org

6. Herceptin Summary of Product Characteristics. Date of revision of text: September 2008. www.medicines.org.uk

7. Roche, data on file. Double Helix development study. Market research. May - June 2008

8. Roche, data on file. Genactis study. Market research. Q4 2007

9. Benson AB et al. Recommended guidelines for the treatment of cancer-induced diarrhea. J Clin Oncol 2004; 22 (14): 2918-2926

10. De Placido S et al. Lapatinib Expanded Access Program (LEAP): Design, operation, and initial study. San Antonio Breast Cancer Symposium 2007. Abstract 6077. www.sabcs.org

11. Bartsch R et al. Capecitabine and trastuzumab in heavily pretreated patients with metastatic breast cancer. J Clin Oncol 2007; 25 (25): 3853-3858

12. Menard S on behalf of the Demetra Group. Observational Demetra study: survival of metastatic breast carcinoma patients after treatment with trastuzumab. J Clin Oncol 2008; 26 (May 20 suppl): Abs 1062

13. Antoine EC et al ECCO 2007, Abs O#2099

14. Jackisch C et al Breast Cancer Res Treat 2007; 106 (Suppl 1): S186, abs 4059;

APPENDIX 1

Table A. Breakdown of the sample of respondents

Specialty	N	PCRs (6 per respondent)	*EBC PCRs*	MBC PCRs
Medical oncologists	41	246	*123*	**123**
Clinical oncologists	44	264	*132*	**132**
Breast surgeons	15	90	*90*	**-**
TOTAL	100	600	*345*	**255**

Breakdown of cancer networks that the recruited respondents in the Double Helix Development market research study belong to.

Anglia Cancer Network (5)
Arden Cancer Network (1)
Avon, Somerset & Wiltshire Cancer Network (2)
Central South Coast Cancer Network(2)
Derby/Burton Cancer Network (2)
Dorset Cancer Network(1)
Essex Cancer Network (3)
Greater Manchester & Cheshire Cancer Network (5)
Greater Midlands Cancer Network (5)
Humber & Yorkshire Coast Cancer Network (3)
Kent Cancer Network (3)
Lancashire & South Cumbria Cancer Network (2)
Leicestershire Cancer Network (2)
Merseyside & Cheshire Cancer Network (5)
Mid Trent Cancer Network (4)
Mount Vernon Cancer Network (2)
North East London Cancer Network (1)
North London Cancer Network (2)
North Trent Cancer Network (3)
North Wales Cancer Service (2)
Northern Cancer Network (10)
Pan Birmingham Cancer Network (4)
Peninsular Cancer Network (2)
South East London Cancer Network (2)
South Wales Cancer Service (2)
South West London Cancer Network (2)
Surrey, West Sussex & Hampshire Cancer Network (3)
Sussex Cancer Network (4)
Thames Valley Cancer Network (2)
Three Counties Cancer Network (4)
West London Cancer Network (3)
West of Scotland Cancer Network (2)
Yorkshire Cancer Network (5)

APPENDIX 2

The GBG-26 trial was incorporated into the Breast International Group (BIG) portfolio and given the label BIG 3-05.

BIG is an international non-profit organization for academic breast cancer research groups from around the world. By encouraging interaction and cooperation between its members and other academic networks, and by collaborating with, but working independently from, the pharmaceutical industry, BIG's mission is to facilitate breast cancer research internationally and optimally serve those affected by the disease. Created by leading European opinion leaders in 1996, BIG now constitutes a network of over 40 groups based in Europe, Canada, Latin America, and the Asia-Pacific region. These research entities, which coordinate the BIG trials, are in turn tied to approximately 3000 specialised hospitals and research centres around the world.