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BY E-MAIL

Dear Eloise,

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 Appraisal Consultation Document (ACD) for the above technology appraisal. Roche has several comments to make on the ACD outlined below under the 3 standard headings.

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

a) Clinical effectiveness of trastuzumab in 2nd line metastatic breast cancer patients

A randomized control trial has now reported results comparing Trastuzumab+Capecitabine with Capecitabine monotherapy in 156 patients with HER-2 positive metastatic breast cancer following progression with trastuzumab treatment. The data from the GBG-26 study was recently presented in a poster at the 44th ASCO Annual Meeting 2008 by *Von Minckwitz* et.al (2008). The OS and TTP results reported in this study provide a more robust evaluation of the efficacy of trastuzumab compared to the pooled non-RCT study results previously considered by the appraisal committee.

The pooled analysis of eight non-RCT Trastuzumab-based studies presented within the manufacturer submission reported a weighted TTP median of 21.8 weeks for trastuzumab. The recent GBG-26 RCT illustrates that the Trastuzumab+Capecitabine combination therapy median TTP was 35.5 weeks (8.2 months). The TTP Hazard Ratio reported in this study for trastuzumab was 0.69 (two-sided p=0.034; one-sided p=0.017).

The trastuzumab arm within the GBG-26 demonstrated an additional 5.1 months overall survival with a HR=0.76 (two-sided p=0.26; one-sided p=0.13), although this is not yet

statistically significant.

Table 1: Comparison of hazard ratios from GBG-26 and EGF100151 studies.

	GBG-26	Lapatinib SmPC (September 2007 follow up)	IRC assessment (April 2006 follow-up)
HR (TTP)	0.69 (95% CI 0.49, 0.97)*	0.72 (95% CI 0.57, 0.91)	0.57 (95% CI 0.43, 0.77)
HR (OS)	0.76 (95% CI 0.47, 1.22)*	0.90 (95% CI 0.71, 1.12)	0.78 (95% CI 0.55, 1.12)

**Derived by Roche from published GBG-26 p-values*

The above efficacy data provides strong evidence to question the assumption and conclusion within the manufacturer's submission that lapatinib is more clinically effective when compared to trastuzumab. The above analysis in fact suggests the opposite, with trastuzumab demonstrating a larger treatment effect over the common comparator capecitabine, when compared to the most recent follow-up data for lapatinib.

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) Validity of trastuzumab as a comparator technology

Roche believe that trastuzumab is not a relevant comparator in the relapsed metastatic breast cancer setting following prior treatment with trastuzumab. This is for the following 2 reasons:

a) Trastuzumab accounts for a small share of current treatment within the specific population of interest, as substantiated by clinicians in section 4.9 of the ACD.
b) Trastuzumab is not included as a relevant comparator within the final scope for the appraisal, developed following consultation and a scoping workshop

Roche has recently commissioned a substantial piece of market research data[1] of 222 patient records covering 33 of the Cancer Networks within the UK. All 222 patients were previously treated with trastuzumab in the metastatic setting and their subsequent treatment following progression captured. The analysis reported that of the 222 HER 2 patients evaluated, who received trastuzumab in the first line metastatic breast cancer setting; only 26 patients (12%) received trastuzumab following disease progression. This analysis confirms the clinical testimony presented to the appraisal committee, that trastuzumab within the population of interest for this evaluation is not standard of care within the NHS.

At present with a high degree of certainty, lapatinib has failed to demonstrate cost effectiveness compared to both capecitabine and vinorelbine. Therefore to demonstrate the

[1] Herceptin Patient Case Record Research, Double Helix Development, June 2008

cost effectiveness of lapatinib compared to trastuzumab is of limited relevance given the stated efficiency objectives of NICE. If positive guidance were published for lapatinib on the basis it demonstrated cost effectiveness compared to trastuzumab, it would lead to the possibility of lapatinib being potentially utilised when 2 more cost-effective alternative treatments were available (xeloda and vinorelbine).

b) Price of Lapatinib

The price of Lapatinib used in the base-case cost effectiveness calculations within the manufacturer's submission do not appear consistent with the latest unit cost of Lapatinib reported[2]. In the base case scenario the price of one Lapatinib tablet is assumed to be £11.00. The price of Lapatinib reported is £804.30 per 70 tablets meaning that each tablet costs £11.49, as confirmed in section 2.3 of the ACD. The difference in price per tablet translates to £2.45 additional cost per day of treatment which in turn translates to £894.25 additional cost for every year of treatment. Although a variation in price for each Lapatinib tablet has been considered in scenario 1[3], the impact of the additional cost for each day of treatment has not been accurately reflected within the base case estimates of the cost effectiveness of lapatinib.

c) Lapatinib phase III RCT follow-up period

Roche believe the clinical effectiveness of lapatinib has been overestimated in the cost-effectiveness calculations through the application of less mature clinical trial data from the lapatinib phase III RCT. Roche would highlight to the Committee that a more recent follow-up of the lapatinib phase III clinical data is available (September 2007 compared to April 2006). The September 2007 follow-up illustrates that the treatment effect of lapatinib compared to capecitabine is not as large when compared to the earlier less mature follow-up data utilised in the cost effectiveness calculations for both the TTP and OS endpoints.

Table 2: Comparison of efficacy by follow-up in EGF100151

	Lapatinib SmPC (September 2007 follow up)	IRC assessment (April 2006 follow-up)
HR (TTP)	0.72 (95% CI 0.57, 0.91)	0.57 (95% CI 0.43, 0.77)
HR (OS)	0.90 (95% CI 0.71, 1.12)	0.78 (95% CI 0.55, 1.12)

The hazard ratio of the overall survival currently used in the effectiveness calculations is 0.78 (95% CI 0.55 to 1.12; p=0.177). The hazard ratio calculated using the longer follow-up data is 0.90 (95% CI 0.71 to 1.12; p=0.3). Likewise the TTP hazard ratio demonstrates a reduced treatment effect in the longer follow-up data for lapatinib, increasing from 0.57 to 0.72.

d) Comparative cardio-toxicity of lapatinib and trastuzumab

Roche considers the following statement in section 4.5 of the ACD an unfair representation of the available clinical evidence: *"The committee agreed that the currently available evidence suggests that cardio-toxicity was less of a problem with lapatinib treatment"*. The

[2] National electronic Library for Medicines
[3] Manufacturer's Submission

statement fails to give adequate consideration or necessary qualification relating to the confounding effect of patient inclusion criteria within the relevant studies. The EGF100151 screened out many patients with the potential to develop HER2 related cardiac dysfunction due to the requirement for previous trastuzumab therapy and the additional inclusion criteria within the EGF100151 study for LVEF to be within the institution's normal range i.e. patients with pre-existing heart disease are excluded. Consequently to compare the cardio-toxicity outcomes naively across studies performed in 2 different populations / lines of therapy is not a fair representation of the comparative side effect profile of the two interventions.

e) 3-weekly trastuzumab drug administration schedule

An audit of 1064 electronic case assessment forms in 2007 covering all Cancer networks[4] provided evidence that 98% of first line and 92% of second line metastatic breast cancer patients receiving trastuzumab received a 3-weekly drug administration schedule. This evidence supports the expert testimony presented to the committee that a 3-weekly regimen is standard of care within the UK and the most appropriate assumption to inform any economic evaluation.

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

Correct recommendation following evaluation of multiple comparators

Based on the analysis of available evidence we believe the recommendations within the ACD are appropriate. Firstly a comparison of trastuzumab with lapatinib is not relevant given the available evidence of current treatment practice within the NHS. Secondly even if the comparison was considered a valid decision problem, the available evidence suggests that such an economic evaluation would simply determine the 3rd or 4th ranked cost effective treatment when including Xeloda and vinorelbine as relevant comparators.

4 ARE THERE ANY EQUALITY RELATED ISSUES THAT NEED SPECIAL CONSIDERATION THAT ARE NOT COVERED IN THE ACD?

No comments

Yours sincerely,

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[4] Breast Cancer Patient level Study Wave 5, Genactis, Roche data on file, 2007