31 March 2010

NHS
National Institute for
Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

www.nice.org.uk

Dear [redacted]

Re: Single Technology Appraisal – Bevacizumab in combination with a taxane for the first-line treatment of metastatic breast cancer

The Evidence Review Group (ERG; NHS Centre for Reviews & Dissemination and Centre for Health Economics - York) and the technical team at NICE have now had an opportunity to take a look at the submission received on the 8th March 2010 from Roche. In general terms they felt that it was well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data.

Both the ERG and the technical team at NICE will be addressing these issues in their reports.

We request you to provide a written response to this letter to the Institute by **17:00, 16th April 2010**. Two versions of this written response should be submitted; one with academic/commercial in confidence information clearly marked and one from which this information is removed.

Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise, and all information submitted under 'academic in confidence' in yellow.

If you present data that is not already referenced in the main body of your submission and that data is seen to be academic/commercial in confidence information, please complete the attached checklist for in confidence information.

Yours sincerely

[redacted]
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Points for clarification

Detailed below are comments/points of clarification on the submission structured by section. Please note that all questions on the effectiveness data are priority questions. Priority questions in the cost-effectiveness section have been noted as such.

Section A: Clarification on effectiveness data (all priority questions)

Background

A1. Please provide additional background information regarding which regimens are currently used in UK clinical practice (and how widely these are used) for first line treatment, for example using descriptive data from IMS Oncology registry. Comment on whether there may be situations where particular treatments (or regimens) may not be considered to be relevant comparators (for example frailer patients or those intolerant of particular regimens).

Participants

A2. [P82] Consort flow chart for study E2100: The status of 11 patients in the paclitaxel monotherapy arm and 38 patients in the paclitaxel/bevacizumab group was not stated. For example, the total number of patients who received paclitaxel monotherapy is stated as 344, but the total accounted for at follow-up (including those lost) is stated as 333. Please provide information on these patients.

A3. [P105] Please provide further justification for including studies with >50% HER2-negative patients in the indirect comparison, given that this criterion is >90% in the direct comparison.

A4. [P106] Selection criteria for the indirect comparison state that trials with ≥60% of patients receiving second or later line treatment were excluded. Please provide justification for setting this threshold at 60%.

A5. [P124] Please provide justification for combining the included trials in the indirect comparison, given the observed variation in baseline characteristics presented in Table 19.

A6. [P124] The selection criteria state that >50% of study participants must be HER-2 negative for inclusion in the indirect comparison. However, Table 19 states that the proportion of HER-2 negative patients was not reported in the Albain, CALGB, or Jones studies. Please clarify why these studies were included in the indirect comparison.

Interventions

A7. Please provide full intervention details for the E2100 study, including the dosage and number of treatment cycles received in each study arm, number of patients in each arm who discontinued any of the treatments, details of any co-interventions and the number of patients crossing over between treatment arms.

A8. [P77] Please provide complete data for the subgroup of relevant patients from the RIBBON-1 trial.

Comparators

A9. The ERG has been advised that 100mg/m^2 of docetaxel is used in UK clinical practice. Please provide comprehensive details and data for the AVADO study.

Outcomes

A10. [P83] Please clarify if more recent follow-up data are available from the E2100 study than those presented in the submission. If more recent analyses are available, please provide these in full.

A11. [P92] Based on the E2100 trial, please report the median progression-free survival (PFS) for Bev-Pac and Pac alone for each of the subgroups reported in Figure 4.

A12. Please provide tabulated data on treatment efficacy for each arm in all trials included in the indirect comparison.

A13. [P87] Please provide further justification for imputing FACT-B values of zero for patients who had disease progression.

A14. Please provide safety data reported in the AVADO trial and also for patients receiving bevacizumab and docetaxel in the RIBBON-1 trial.

A15. [P101] Please confirm that Table 18 shows the means of the 'raw data' for FACT-B, as collected within the E2100 trial, without any adjustments for missing data. Please confirm whether a negative value of the statistic used (change from baseline) indicates a 'better' or 'worse' result. Please provide the baseline scores (TOI-B and TOT-B) of the FACT-B measure.

A16. [P101] Please clarify the number of patients completing the QoL questionnaire at each stage of the E2100 study (baseline, 17 weeks, 33 weeks) and how these numbers correspond to those reported in Figure 2 (p.82). Please give reasons for censoring/missing data at various time points in the QoL data. Can it be shown that there was no informative censoring/missing data? If available, please provide summary characteristics for those patients who did not complete QoL questionnaires at each time point.

Additional Issues

A17. Please provide details of the intention to treat (ITT) approach used in the analysis of the E2100 trial (e.g. last observation carried forward, imputation), and whether the approach differed for different outcomes.

A18. Please provide further methodological and technical details for the indirect comparison analysis (including formulas used and any software packages used to calculate the pooled estimates).

A19. Please clarify how the studies were initially selected for inclusion in section 6.2, prior to the full inclusion criteria listed in 6.2.2 being applied.

A20. [P77] Please provide details of the reasons for exclusion of the 266 non-RCT studies in Figure 1.

A21. [P106] The submission states that 'trials with <100 patients receiving a relevant study treatment were excluded' from the indirect comparison. Please provide details of the 12 records excluded on this basis.

Section B: Clarification on cost-effectiveness data

Comparators in the evidence synthesis and economic analysis

B1. **Priority question:** Please consider approaches to formally incorporate the following comparators into the existing economic analysis and present the results of these analyses:

- 3-weekly paclitaxel monotherapy
- Bevacizumab + docetaxel

If information derived from clinical trials other than the E2100 is used, please provide detailed input data sources and assumptions.

B2. **Priority question:** The base-case model assumes that the regimens paclitaxel, docetaxel, and gemcitabine + paclitaxel are equally effective. As an alternative scenario, please re-run the cost effectiveness analysis using the results of the evidence synthesis (disregarding issues of statistical significance).

Time on treatment

B3. **Priority question:** [P156-157] Please provide estimated coefficients, standard errors (SE) and variance-covariance matrices for all parametric functions used in fitting these data (as reported in Tables 29 and 30).

B4. [P156-157] Please report the mean [and SE or 95% confidence interval (CI)] of the time to off drug for bevacizumab and paclitaxel (for the Bev-Pac arm and the Pac alone arm of the E2100 trial) based on both the Kaplan Meier curves [e.g. by using the area under the curve (AUC) method] and the parametric functions fitted to the data.

Progression-free survival (PFS)

B5. [P169, Figure 13] Based on the E2100 trial, please provide the following from the Kaplan Meier analysis (and thus for every time point a failure has occurred or at regular time points, for example monthly) for each arm of the trial.

- Number at risk over time
- Proportion of 'survivors' over time
- Confidence intervals for each of these proportions

B6. **Priority question:** [P171, Table 34 and Figure 13] Please provide estimated coefficients, standard errors and variance-covariance matrices for all parametric functions reported in Table 34. Please provide a figure showing the predicted PFS estimates for all parametric functions superimposed with the Kaplan Meier estimates.

B7. **Priority question:** Please report the mean (and SE or 95% CI) time to PFS for the regimens Bev-Pac and Pac alone based on both the Kaplan Meier curves (e.g. using AUC calculations) and the parametric functions considered.

B8. Please provide the results of statistical tests (or graphs) to justify the assumption of proportional hazards when analysing PFS.

Overall survival (OS)

B9. [P170, Figure 14] Please provide the equivalent information requested in B5 for overall survival.

B10. **Priority question:** Please model OS using a similar approach to PFS (i.e. not combining the individual trial arms). If the assumption of proportional hazards does not hold, please fit independent survival curves to each arm separately. For all models and parametric functions fitted, please provide point estimates, standard errors and variance-covariance matrices for the regression coefficients and/or parameters of the distributions.

B11. **Priority question:** Please report the mean (and SE or 95% CI) OS assumed for the regimens Bev-Pac and Pac alone based on the following approaches:

- The OS estimates for Bev-Pac and Pac alone derived from the economic model.
- The OS estimates for Bev-Pac and Pac alone derived from the separate Kaplan Meier curves reported in Figure 14 (e.g. using AUC estimates)
- The OS estimates for Bev-Pac and Pac alone based on the alternative parametric functions (either assuming proportional hazards or based on fitting individual survival curves, i.e. derived from B10)

Time from progression to death

B12. **Priority question:** [Figure 16, P174] Please model time from progression to death separately for each arm. Please conduct an additional scenario of the cost effectiveness model using this approach.

B13. [Figure 16, P174] Please provide additional justification to support the assumption of a constant hazard of death (over time). Please consider fitting alternative parametric functions to these data and provide the results (point estimates, SE and variance-covariance matrices for the coefficients and other relevant parameters).

Resource use

B14. Please report the following:

- The mean number of chemotherapy cycles (and SE) in the E2100 study for each treatment in each arm

- Descriptive statistics from the E2100 study reporting the proportion of patients receiving 0,1,2,3,4,5,… chemotherapy cycles for each treatment in each arm

- The mean number of cycles assumed in the economic model for each treatment of each regimen

B15. Please provide further justification for the costs of second-line therapies following progression. Please detail relevant protocols followed in UK clinical practice and comment on the impact on cost effectiveness of considering higher costs after progression.

QoL

B16. [P101] Please state whether a mapping algorithm was searched for and considered to estimate EQ-5D from the FACT QoL instrument, in order to estimate utility at baseline and each follow-up in each treatment group.

Subgroup and sensitivity analyses for the survival regressions and economic model

B17. The economic model finds that the difference in overall life expectancy between Bev + Pac compared with Pac is about 4 months (Table 55). This is considerably greater than the results of the E2100 RCT, which shows a much lower, non-significant difference in overall life expectancy (Figure 5). Please provide further explanation for this difference between the model and the RCT, and consider providing a sensitivity analysis where the parameters are estimated or calibrated to fit more closely with the trial data.

Relevance of other economic evaluations

B18. [P151, Table 27] The submission found other cost-effectiveness analyses, but stated that they were not relevant as they were all conducted outside the UK. The ERG considers that as there are very few published economic evaluations these may be of interest to the Committee. Please briefly review the main methods and results of the full economic evaluations (i.e., that compare both costs and outcomes of two or more relevant interventions) and compare these to the results of the current study.

<u>Section C: Textual clarifications and additional points</u>

C1. [Figure 16, P174] The labelling at the foot of Figure 16 is difficult to understand. The Pac + Bev label seems to be missing. Please clarify which curve represents which treatment.

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