13th August 2009

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Dear [redacted],

Re: Single Technology Appraisal – Bevacizumab in combination with oxaliplatin and either 5FU or capecitabine for the treatment of metastatic colorectal cancer

The Evidence Review Group (ERG), School of Health and Related Research (ScHARR) Sheffield University and the technical team at NICE have now had an opportunity to take a look at submission received by Roche. In general terms they felt that it is well presented and clear. However, the ERG and the NICE technical team would like further clarification relating to the clinical and cost effectiveness data. We have indicated which questions carry a higher priority but at the same time stress the need for Roche to address all listed questions.

Both the ERG and the technical team at NICE will be addressing these issues in their reports. As there will not be any consultation on the evidence report prior to the Appraisal Committee meeting you may want to address the points raised and provide further discussion from your perspective at this stage.

We request you to provide a written response to this letter to the Institute by **17:00, Thursday 27th August 2009**. 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 red, 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.

If you have any further queries on the technical issues raised in this letter then please contact Elangovan Gajraj (elangovan.gajraj@nice.org.uk) – Technical Lead). Any procedural questions should be addressed to Philip Higham – Project Manager (Philip.higham@nice.org.uk) in the first instance.

Yours sincerely

Meindert Boysen
Programme Director Technology Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. **Priority question**: Section 6.7.1. Please clarify whether NO16966 trial uses the most effective chemotherapy combination (schedule, dosage and timing) of FOLFOX-4 and XELOX. In addition, do the schedule, dosage and timings in the NO16966 trial reflect current practice in (or outside) the UK for first line therapy?

A2. **Priority question**: Section 6.7.5.1. The validity of combining the two parts of the study may be questioned. Please provide the statistical rationale for pooling of patients receiving chemotherapy alone (XELOX or FOLFOX) in the two arm open label study with those receiving FOLFOX or XELOX plus placebo in the 2x2 factorial design. In addition, please clarify how you have accounted for between study variability in the estimate for the baseline treatment mean for patients receiving chemotherapy alone (XELOX or FOLFOX) with those receiving FOLFOX or XELOX plus placebo and how you have preserved the randomisation of the two study designs (two arm design and 2x2 factorial design) when estimating population treatment effects.

A3. **Priority question**: Section 6.8.1.1. Although a statistically significant treatment action (p=0.7025) was ruled out in the 2x2 factorial trial, a high p-value could reflect low power and so cannot be taken as evidence for no interaction (Montgomery et al BMC Medical Research Methodology 2003, 3.26; available at http://www.biomedcentral.com/1471-2288/3/26). Did the N016966 trial have sufficient power to detect an interaction between each treatment group? If the trial had sufficient power to detect a difference between treatments, could you please provide a power curve and further details on the test for interaction including 95% confidence intervals etc.

A4. **Priority question**: Section 6.8.1.2. Please provide tabulated results (ITT analysis) for each of the six treatment groups separately for 1) progression free survival, 2) overall survival and 3) tumour response (including Kaplan-Meier curves with numbers at risk and failures). Ideally data should be reported as follows: median follow up, event rates (number of events/total number) for each arm separately. In addition, provide hazard ratios, confidence intervals and p-values for all (i.e. 15) pairs of treatment groups.

A5. **Priority question**: Section 6.11. Please provide adverse event (tabulated results) data for each of the six treatment groups separately for 1) all grade adverse events 2) serious adverse events (grade 3/4).

Also provide details (tabulated, if applicable) on the following 1) compliance to study treatment 2) rates/reasons of treatment discontinuation (including adverse events leading to discontinuation of trial treatments) and 3) number of patients treated until progressive disease, for each of the six treatment groups separately. In addition what was the mean/median duration of treatment with bevacizumab and how does this compare with other trials?

A6. We request further details on the systematic review as follows:

- Section 6.6. Please could you clarify if data selection (provide kappa agreement scores, if applicable) and abstraction was taken independently by two reviewers and how any disagreements were resolved.

- Section 6.6.2. Please could you clarify the inclusion/exclusion criteria in terms of the population, interventions, comparators, outcomes and study design?

- Section 6.6.3. As stated in section 6.2.3 of the STA specification for Manufacturer Submission of Evidence '…a flow diagram of the number of studies included and excluded at each stage should be provided…as per the QUORUM statement flow diagram." Can you provide a QUORUM flow diagram?

- Section 6.7. As stated in section 6.3 of the STA specification for Manufacturer Submission of Evidence '… items 2 to 14 of the CONSORT checklist should be provided… where there is more than one RCT, the information should be tabulated'. Can you provide a tabulated summary of the included RCTs according to items 2 to 14 of the CONSORT checklist?

- Section 6.14.3. Please provide further details on whether a systematic review of non-RCTs was undertaken by the manufacturer? if so, how was this done (including details of identification and selection, critical appraisal [relevant checklist] and data synthesis)?

A7. Section 6.7.6. As stated in the Summary of Product Characteristics, the recommended dose of bevacizumab, administered as intravenous infusion, is either 5 or 10 mg/kg of body weight given once every two weeks or 7.5 or 15 mg/kg of body weight given once every 3 weeks. In the NO16966 trial the doses of bevacizumab studied were 7.5mg/kg every 3 weeks (XELOX) and 5mg/kg every 2 weeks (FOLFOX-4). In the ECOG E3200 trial the dose of bevacizumab was 10mg/kg every 2 weeks. Please provide evidence on the efficacy of the higher dose in first line use and the lower dose in second line use.

A8. Section 6.8.2. Please provide further details (including tabulated results by each treatment group; reference sources; was it a priori or post hoc

analysis), on the subgroup analyses in patients with liver metastases in the NO16966 trial and any other supportive evidence.

A9. Can you provide supportive evidence for your assumption of equivalence for the following regimens

- FOLFOX and FOLFIRI
- FOLFOX and XELOX
- FOLFOX-6 and FOLFOX-4

Section B: Clarification on cost-effectiveness data

B1. **Priority question**: Section 6.8.1, As noted earlier, the validity of combining the two parts of the NO16966 trial may be questioned (The NO16966 effectively consists of two separate trials: the first being XELOX vs. FOLFOX and the second having four arms XELOX+placebo/Bev and FOLFOX+placebo/Bev). As the base-case (i.e. please use this for all subsequent sensitivity analyses) please use the data from the 2x2 factorial part of the trial to calculate survival as presented in Saltz et al 2008. Please provide possible reasons why survival was better in the XELOX/FOLFOX+placebo arms compared to the XELOX/FOLFOX arms.

B2. **Priority question**: Section 6.8.1. The true relative risk of adding bevacizumab may differ when added to XELOX rather than FOLFOX, also the underlying efficacy of XELOX and FOLFOX may be different. Please perform a sensitivity analysis in which the XELOX and FOLFOX arms are not pooled.

B3. **Priority question**: Section 7.2.6.8. After the median follow-up time of 28 months for overall survival (OS) there were 14% (96) and 16% (211) remaining in the XELOX/FOLFOX and XELOX/FOLFOX+Bev arms respectively. Please clarify why the data after median follow-up was not included in the modelling even though the method of fitting the parametric curves to survival data should allow for the greater uncertainty present in the tail of the curve. Please use the whole data set to fit the curve in the base-case analysis and also present a graph comparing the entire Kaplan-Meier curve to the fitted parametric curve.

B4. **Priority question**: Section 7.2.6.8. The three phases of the progression free survival (PFS) curve described on p119 may be somewhat subjective. In addition, it is not clear why an exponential function rather than a Weibull function is appropriate as this seems inconsistent with the approach taken for overall survival (OS). Please fit a Weibull curve to the PFS data from month 6 onwards and use this in the base-case analysis.

B5. **Priority question**: Section 6.8.2. On p71 the impact of adding bevacizumab to oxaliplatin-based chemotherapy in patients with liver metastases in trial NO16966 is discussed. If possible, please evaluate the cost effectiveness of adding bevacizumab in this group as a subgroup analysis.

B6. **Priority question**: Section 7.2.1.2. On p105 of the manufacturer's submission it states that in the N016966 trial, treatment with bevacizumab was often stopped at the same time point as the base chemotherapy was stopped. Please provide data on the number of patients for whom treatment with bevacizumab continued after chemotherapy was stopped. Our clinical advisors suggest that in practice chemotherapy treatment would be likely to be stopped gradually rather than all at the same time. For example, oxaliplatin may be stopped initially and other drugs continued. Please clarify whether all treatment was stopped at the same time in the trial. Please provide details of the number of persons in the trial who continued receiving bevacizumab for over 1 year.

B7. **Priority question**: Our clinical advisors suggest that in practice treatment may be stopped and then restarted a few months later if toxicity (e.g. oxaliplatin) became a problem. As an example, for a patient receiving treatment for 6 months, then having a 3 month break, then continuing on treatment, how would the APAS scheme be applied? Would the continuation of treatment still be regarded as first line?

B8. **Priority question**: Section 7.2.9.1. Our clinical advisors suggest that the addition of bevacizumab is unlikely to reduce the incidence of adverse events. The incidence of neutropenia/granulocytopenia is 44% with FOLFOX and 2% with FOLFOX+Bev. Similarly the incidence of diarrhoea, nausea/vomiting, and neurotoxicity were seen to be lower in the +bevacizumab arms. Please perform a sensitivity analysis in which the incidence of the non-bevacizumab related adverse events is the same with and without bevacizumab (To further clarify the Evidence Review Group recommends that adverse event incidence figures from the XELOX and XELOX+bev arms are pooled for the non-bevacizumab specific adverse events).

B9. **Priority question**: Section 7.2.8.3. Please clarify whether a systematic review was performed to obtain data on utility values. Please provide references for the original sources of the utility values used in the modelling and provide details of any assumptions made. Please include the source of the lower and upper values for the utility values used in the sensitivity analyses. On p115 Bidard et al 2008 is referenced, please clarify as there is no mention of quality of life in the abstract.

B10. **Priority question**: Section 7.2.8.3. A review of utility values for CRC (Sharp et al 2009, www.hiqa.ie/publications.asp) indicates a much wider range than is reported in the submission. Please compare the values used in the manufacturers submission to those values for

metastatic CRC reported in Sharp et al 2009 (specifically Ness 1999, van den Brink 2004, Stouthard 2000) and provide a commentary to justify the choice. It is suggested that an additional sensitivity analyses may be required using values from Sharp et al 2009.

B11. **Priority question**: Section 7.3.3. Please present the following results of the probabilistic sensitivity analyses: The mean and 95% CI for the incremental costs, the incremental QALYs and the ICER.

Comparison	FOLFOX+Bev vs. FOLFOX	B-XELOX vs. XELOX	and B-XELOX vs. FOLFOX
Incremental Costs: mean	£6,848		
95% percentiles	(£5,647, £6,848)		
Incremental QALYs: mean	0.1649		
95% percentiles	(0.0890, 0.2397)		
Incremental cost per QALY gained (mean Incr. costs / Incr. QALYs)	£41,518		
95% percentiles of ICERs	(£31,136**,** £67,859)		

B12. Section 7.2.3. On p165 it states that market research surveyed 50 oncologists across England and Wales but table 14 on p108 suggests that there were 38. Please clarify the sample size and methods used in the market research undertaken, and discuss whether this sample is likely to be representative.

B13. Could you please clarify the following regarding the economic model

- Section 7.2.6.8. In the base case, a treatment effect is assumed to continue beyond median follow-up. There is an option to include no treatment effect after median follow up. Please clarify what this assumption means and explain how this was implemented in the model.

- Section 7.2.6.8. The parameter values presented in Table 25 p122 do not match the parameter values in cells C34 and C35 on the parameter estimates sheet of the model. Please clarify which values are correct.

- Section 7.2.6.1. Please include drug wastage costs for oxaliplatin within the modelling of drug costs p116.

- Section 7.2.6.8. A hazard ratio is applied to the FOLFOX PFS and OS survival curves to derive curves for FOLFIRI. It is not clear if this applies only to the extrapolated part of the FOLFOX curves (beyond 28 months) and how the HR is applied to the earlier non-extrapolated portion of the KM curve

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B14. Section 6.10. As head to head data was available, a mixed treatment comparison (MTC) was not required or undertaken by the manufacturer. However, the manufacturer provided supportive evidence from an MTC undertaken by Golfinopoulos et al. 2007. On p75 the manufacturers submission suggest that the MTC meta-analysis included results from the ECOG E3200 trial (second line setting) but did not include data from the NO16966 trial (first line setting). The Evidence Review Group notes that the MTC meta-analysis by Golfinopoulos et al (2007) included the results from the NO16966 trial with specific reference to Salt et al 2007 (Proc Am Soc Clin Oncol; 25 (170S suppl): abstr 4028). For completeness please clarify what data (e.g. which arms from the trial) from the NO16966 trial was included.

B15. Could you please clarify the following points regarding the economic analysis

- Section 7.2.9. Please provide 95% confidence intervals for the mean dose values in Table 29 p133 and mean number of cycles per month observed in Table 33 p137. In addition, please provide for each of the six treatment groups separately. Table 29 on p133 describes a mean dose of bevacizumab for the XELOX and FOLFOX arms. Please clarify, as these arms should not involve any bevacizumab.

- Please justify the assumption that people in the PFS state post-treatment have a utility equal to healthy people in the general population.

- Section 7.2.9.1. In table 35 on p 139 the incidence of adverse events is described. In the Saltz et al 2008 paper adverse events of special interest to bevacizumab with incidence greater than or equal to 2% were venous thromboembolic events, hypertension, bleeding, and arterial thromboembolic events (including ischemic cardiac events). Please clarify why bleeding and arterial thromboembolic events were not included in table 35 on p139. In table 34 on p139 the unit costs for adverse events are described with references. Please include in this table the procedure/treatment/drugs which are included in these costs.

- Section 7.3.3. The scale on the x-axis of Figure 25 CEAC makes it unclear and difficult to interpret. Please provide Figure 25 using the intervals £0K, £10K, £20K etc on the x-axis.

B16. Could you please clarify the following information in the appendices

- Appendix E1. As the model submitted by the manufacturer is a cohort model the mean costs of treatment are appropriate. Please clarify whether the costs have been sampled using the quartiles described in table 51 on p182 and in table 52 rather than the standard error of the mean, which would be incorrect.

- Appendix E3. The manufacturer's submission states that a Beta Pert distribution was used to estimate uncertainty in adverse event costs. It is unclear whether the quartiles listed in Table 51 or the 50% and 150% of the mean were used as the low and high estimates. Please describe how the parameters for the beta pert distributions were calculated. Please also describe any assumptions made, including how the mode was estimated.

- Appendix E3. For the PSA a Beta (utility*1000, (1-utility)*1000) distribution was used to model the uncertainty in the utility values. Please use a Beta distribution that fits to the confidence intervals of the utility data.

Section C: Textual clarifications and additional points

C1. **Priority question**: The statement "the comprehensive safety data collected in study NO16966 and elsewhere, and meta-analysed by Cao et al (2009), demonstrated that B-XELOX and B-FOLFOX has similar tolerability to FOLFOX and XELOX" appears to be selectively reported and misleading. The meta-analysis by Cao et al (2009) also highlighted that a higher incidence of grade 3/4 adverse events, hypertension, thromboembolic /thrombotic events; bleeding and gastrointestinal perforation was associated with chemotherapy plus bevacizumab compared with chemotherapy alone. The Evidence Review Group also notes that more recent meta-analyses have also found an increased risk of gastrointestinal perforation (Hapani et al. Risk of gastrointestinal perforation in patients with cancer treated with bevacizumab: a meta-analysis. Lancet Oncol 2009; 10: 559-568) and venous thromboembolism (Nalluri et al. Risk of Venous Thromboembolism with the Angiogenesis Inhibitor Bevacizumab in Cancer Patients - A Meta-analysis JAMA. 2008; 300(19):2277-2285) associated with bevacizumab therapy. Please clarify.

C2. Summary points

The base-case analysis requested by the ERG:

- Data from the 2x2 part of the NO19699 trial as presented in Saltz et al 2008

- The data set is not censored at 28 months – all data is used.

- PFS is modelled by fitting a Weibull curve to data from month 6 onwards.

Sensitivity analyses requested by the ERG:

- The XELOX and FOLFOX arms are considered separately.
- Subgroup analyses for patients with and without liver metastases.
- Incidence figures from the XELOX and XELOX+Bev arms are pooled for the non-Bevacizumab specific adverse events.
- Additional sensitivity analyses in relation to utility values, using data from Sharp et al 2009.