19/09/2012

National Institute for Health and Clinical Excellence

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[redacted]

Re: Single Technology Appraisal – Bevacizumab in combination with paclitaxel and carboplatin for the first-line treatment of ovarian cancer

The Evidence Review Group (Southampton Health Technology Assessments Centre) and the technical team at NICE have now had an opportunity to take a look at submission received on the 17 August 2012 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.

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 **12.30, 03 October 2012**. 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.

Please do not 'embed' documents (i.e. PDFs, spreadsheets) within your response as this may result in your information being displaced or unreadable. Any supporting documents should be emailed to us separately as attachments, or sent on a CD.

If you have any further queries on the technical issues raised in this letter then please contact [redacted] Any procedural questions should be addressed to [redacted] in the first instance.

Yours sincerely

[redacted]

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

A1. The primary outcome measure in Study GOG-0218 is PFS based on investigator assessment, please clarify whether this is censored for CA-125 or without censoring.

A2. The primary analysis of PFS in Study GOG-0218 in the EMA/CHMP Assessment report is without censoring and the primary analysis in the manufacturer's submission appears to be censored. Please explain why different results are used.

A3. Please clarify what is meant by final analysis (September 2010, page 79), primary analysis (page 80) and updated analysis (August 2011, page 81) and why there is inconsistency in reporting with different time points for different assessments. For example:

- for the PFS results of the GOG-0218 study, the investigator assessment, censored data has a final analysis date of September 2010 (Table 10, page 80) and updated analysis without censoring date of August 2011 (page 82); however, there do not appear to be updated censored data
- there do not appear to be updated PFS IRC results
- OS updated results are not reported (although they are reported in the NEJM trial publication)
- Subgroup analyses are reported as February 2010 which suggests that there should be later results available for consistency with the primary PFS results (page 82).

A4. Please supply p-values for:

- Updated PFS analysis (for both groups), page 82.
- Table 14, page 84. Comparison of PFS results by disease stage and debulking status from GOG-0218 for the CPP, CPB15 and CPB15+ groups
- All the comparisons between trial groups for each of the 5 time points for the FACT-O TOI results from GOG-0218 (pages 86 – 87).
- Table 20, page 93. Comparison of PFS results by disease stage and debulking status from ICON7 for the CP and CPB7.5+ groups
- Table 23, page 102. Comparisons of exposure to bevacizumab/ placebo and chemotherapy in the GOG-0218 study for the CPP, CPB15 and CPB15+ groups
- Table 30, page 109. Comparisons of the dose and duration of therapy in ICON7 for the CP and CPB7.5+ groups

A5. For the updated PFS analysis (August 2011), please supply the HR and 95% CI for the CPB15 versus CPP comparison and the median PFS months for the CPP, CPB15 and CPB15+ groups (page 82).

A6. Please clarify whether the PFS pre-planned subgroup analyses for both Study GOG-0218 (Table 14) and Study ICON7 (Table 18 and Table 20) are adequately powered to detect a statistically significant difference between

treatment arms for the relevant subgroups. If so please supply details of the power calculation.

A7. For the ICON7 study please explain why the numbers of patients in Stage III suboptimally debulked plus patients in Stage IV presented in Table 20 do not match the numbers presented in Table 18.

A8. In section 1.6 on page 12, it is stated that there are no ongoing or complete studies likely to provide additional evidence in the next 12 months. However, in section 2.6 on page 22 reference is made to "three ongoing studies of carboplatin plus dose-dense or conventional paclitaxel … two of which include concomitant use of bevacizumab". Please clarify which two studies include concomitant use of bevacizumab (i.e. GOG-262, ICON8 or OCTAVIA). Please also clarify the patient populations and doses of bevacizumab examined in these studies and whether or not evidence from these studies is likely to be available in the next 12 months.

A9. Please clarify the method used to impute missing data for the FACT-O TOI measure when fewer than 50% of items were missing on a subscale for a patient (page 67).

A10. On page 68 it is stated that "Following the protocol specifications with modifications, three hypotheses regarding whether FACT-O TOI scores reported by patients during the treatment period over time are independent of treatment received will be tested". Please clarify what modifications were made.

A11. Please clarify whether or not the "exploratory" subgroup analyses in the GOG-0218 study detailed on page 72 were planned or post-hoc analyses.

A12. Please provide information on the relative risk, risk difference and associated 95% confidence intervals for each adverse event in Tables 24 (page 103), 25 (page 104), 26 (page 105), 28 (page 108), 29 (page 108), 31 (page 109), 32 (page 110), and 33 (page 111). Please also provide the same information for the following statement on page 112: "More deaths from adverse events were observed in the two bevacizumab-containing arms … compared with the control arm" for the GOG-0218 study.

A13. On page 103, in the adverse events section, it is stated that Table 25 (page 104) shows adverse events that "showed a ≥5% difference between arms of the GOG-0218 trial". Why are only adverse events with this difference between groups shown? Furthermore, please clarify why only adverse events reported with a ≥10% difference between groups have been commented on as differing between groups – were these the only statistically significant differences in adverse events reported between the groups?

A14. Please provide references for the original sources of the FACT-O TOI, Ovarian Cancer Subscale, and abdominal discomfort score (ADS) quality of life measures used in the GOG-0218 study and for the measures used in the ICON7 study (page 58). Please also provide information or references to sources about their reliability and validity.

A15. Please clarify what is meant by 'MRC endorsed subgroup analysis' from the ICON7 study (page 6).

Section B: Clarifcation on cost-effectiveness data

B1. Please clarify the method, source and probabilities used in the model for the transition between the health states from PFS to death.

B2. Please provide details of the parameter ranges and distributions used for the input parameters in the PSA.