National Institute for Health and Clinical Excellence

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Dear [redacted],

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

The Evidence Review Group Liverpool Reviews and Implementation Group (LRiG) and the technical team at NICE have now had an opportunity to take a look at the submission received on 10 October 2011 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 **17:00, 24 January 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 Christian Griffiths – Technical Lead (Christian.Griffiths@nice.org.uk). Any procedural questions should be addressed to Kate Moore – Project Manager (Kate.Moore@nice.org.uk) in the first instance.

Yours sincerely

Helen Knight
Associate Director – Appraisals
Centre for Health Technology Evaluation

Encl. checklist for in confidence information

Section A: Clarification on effectiveness data

Issues relating to the RIBBON-1 trial

A.1 Please provide a breakdown of the reasons for the patients who withdrew from the blinded follow-up phase in the "other" category in figure 3 (page 49) of the manufacturer's submission.

A.2 On page 45 of the manufacturer's submission, it is stated that "One-year survival rate would be compared only when a statistically significant result is observed in overall survival between two treatment arms." A significant result in overall survival was not observed between the treatment arms and yet one-year survival estimates were still presented. Please explain why one-year survival estimates were presented.

Section B: Clarification on cost-effectiveness data

B.1 **Priority Request:** Modelled survival in progressive disease (PD)

Please provide the following:

a. Details of the models used to represent survival in PD (displayed in Figure 15, page 88 of the manufacturer's submission);
b. The estimated area under the curve for PD, including projections;
c. Percentage of patients who died at progression (i.e. those who didn't enter the post-progression survival [PPS] phase)

B.2 **Priority Request:** Observed survival analyses

Clinical results in the submission do not allow for exploration of issues related to time to events. Please provide the following clinical result analyses (a sample table structure for responses is included at the end of this question):

a. Product-Limit Survival tables (e.g. using SAS LIFETEST procedure) from analysing the RIBBON-1 trial data for time from progression to time of death (PPS)

   by

   - bevacizumab+capecitabine and placebo+capecitabine

   stratified by

   - whether patients did or did not receive further optional bevacizumab following disease progression.

   i.e. 2 x 2 = 4 sets of output.

   In each case, please provide a table of results (see example included at the end of this question) showing for each event time:

   - time of event from baseline (days)
   - product-limit estimate of survival proportion
   - standard error of survival proportion

- number of patients failed
- number of patients remaining at risk

b. In addition, please provide for each set of outputs the estimated mean survival time from baseline up to the time of last event, together with the standard error of the mean estimate.

Example of output (SAS) required from analyses specified in question B2

The LIFETEST Procedure

Product-Limit Survival Estimates						
SURVIVAL		Survival	Failure	Survival Standard Error	Number Failed	Number Left
0.000		1.0000	0	0	0	62
1.000		.	.	.	1	61
1.000		0.9677	0.0323	0.0224	2	60
3.000		0.9516	0.0484	0.0273	3	59
7.000		0.9355	0.0645	0.0312	4	58
8.000		.	.	.	5	57
8.000		.	.	.	6	56
8.000		0.8871	0.1129	0.0402	7	55
10.000		0.8710	0.1290	0.0426	8	54
SKIP…		0.8548	0.1452	0.0447	9	53
389.000		0.1010	0.8990	0.0417	52	5
411.000		0.0808	0.9192	0.0379	53	4
467.000		0.0606	0.9394	0.0334	54	3
587.000		0.0404	0.9596	0.0277	55	2
991.000		0.0202	0.9798	0.0199	56	1
999.000		0	1.0000	0	57	0

B.3 The manufacturer's submission refers to a paper by Zielinski et al 2009 which suggests that for capecitabine 1250mg/m^2 and capecitabine 1050mg/m^2, efficacy is similar but adverse events are reduced at the lower dose. Figure 1 of this paper appears to support the adverse event data by plotting adverse event rates from different studies. If available, please provide pooled data on the incidence of these same adverse events and any other relevant adverse events (such as those listed in Table 28) for capecitabine at a 1250mg/m^2 dose and how these compare with adverse events at the 1000mg/m^2 dose (and if data allows by grade) .

B.4 **Priority Request:** Table 14 (page 82 of the manufacturer's submission) shows patients who received bevacizumab post-progression. For each treatment arm, please provide the number (and %) of patients who received any post-progression therapy and details of the therapies received (including type of treatment and the number of lines of treatment if data is available).

B.5 To adjust for crossover, the Rank Preserving Structural Failure Time (RPSFT) Model is used to estimate overall survival in the economic model (page 83 of the manufacturer's submission).

a. Please justify the use of the RPSFT over other methods that may be used for adjusting for cross-over, such as the Inverse Probability of Censoring Weights (IPCW).
b. Please present overall survival estimates using both the RPSFT and IPCW methods

Section C: Textual clarifications and additional points

Issues relating to the number of patients eligible for bevacizumab in combination with capecitabine (page 18 of the manufacturer's submission)

C.1 Please can you highlight/explain from where in Scarborough et al 2010 the assumption that 96% of patients are not contraindicated for bevacizumab is derived?

C.2 Please can you highlight/explain from where in Dent et al 2007 the assumption that 83% of patients have relapsed more than 12 months after initial anthracycline and taxane treatment is derived?