NHS
National Institute for
Health and Clinical Excellence

NICE
Midcity Place
71 High Holborn
London
WC1V 6NA

Tel: 0161 870 3154
Fax: 020 7061 9792

Email: Kate.Moore@nice.org.uk

www.nice.org.uk

Dear [redacted],

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

The Evidence Review Group Liverpool Reviews and Implementation Group (LRiG) and the technical team at NICE have now had an opportunity to take a further look at the submission received on 10th October 2011 by Roche. A number of additional issues have been identified regarding the subgroup of patients used in the economic model (that is those who had received a prior taxane) and the relevance of this subgroup to the population in the final scope issued by NICE.

It is felt that while the subgroup used in the economic model almost reflects the indication for capecitabine, it is a narrower and more specific population than that specified in the licensed indication for bevacizumab in combination with capecitabine. Capecitabine is indicated for the treatment of metastatic breast cancer after the **failure of taxanes and an anthracycline-containing regimen**, while bevacizumab in combination with capecitabine is indicated for the first-line treatment of those with metastatic breast cancer for whom treatment with other chemotherapy options including **taxanes or anthracyclines is not considered appropriate**.

The ERG and the NICE technical team would like further clarification relating to **either** the clinical effectiveness data for the subgroup used in the economic model accompanying the submission **or,** preferably, additional cost-effectiveness data for the Intention-to treat/safety population in the RIBBON-1 trial.

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, 27th January**. 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 Raisa Sidhu – Technical Lead (Raisa.Sidhu@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

Priority Request: In order of preference, please provide **either** of the following**:**

A1. An appropriate economic model based on the ITT/safety populations of the RIBBON-1 trial addressed in the clinical section of the manufacturer's submission rather than on the subgroup of people who have had a prior adjuvant or neoadjuvant taxane.

a. Please also present a revision of sections 6.2-6.9 of the manufacturer's submission to accompany the economic model based on the ITT/safety population

b. Modelled survival in progressive disease (PD). Please provide the following:

i. Details of the models used to represent survival in PD (as displayed in Figure 15, page 88 of the manufacturer's submission);

ii. The estimated area under the curve for PD, including projections;

iii. Percentage of patients who died at progression (i.e. those who didn't enter the post-progression survival [PPS] phase).

c. 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):

i. Please provide 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

ii. 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 A1.c

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

d. 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).

Or :

A2. For the subgroup of patients who had received a prior taxane, please provide the following for both the bevacizumab + capecitabine and capecitabine arms of the RIBBON -1 trial

a. Baseline characteristics similar to Table 5, page 39 of the manufacturer's submission, and also including data on Region and , numbers of patients from the UK (if data is available)

b. In addition to PFS and OS already provided in the text and figures 6 and 8, of the manufacturer's submission, please present the following analyses:

i. Objective response rate

ii. One-year survival rate

iii. Duration of objective response

iv. PFS based on IRC assessment

v. Adverse events during the blinded phase in a similar format to Table 7 of the manufacturer's submission, and if data is available also for the open-label phase (which the ERG acknowledges may only be available for all patients who received a prior taxane and not by treatment arm)

c. 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).