National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Bevacizumab in combination with capecitabine for the first-line treatment of metastatic breast cancer

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from Liverpool Reviews and Implementation Group LRiG) to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by **5pm, Friday 2 March 2012** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

Issue 1 Acknowledgement of placebo arm of RIBBON-1

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Pages 7-17 and throughout the report The 2 arms of RIBBON1 study are described throughout the ERG report as "BEV + CAPE" and "CAPE". Nowhere in the report does the ERG state that this is a placebo-controlled study (see pages 7-17). In fact patients in the control arm received CAPE + placebo.	The term "CAPE" should be replaced by "PLAC + CAPE" wherever it refers to the placebo arm of the RIBBON-1 study.	The validity of the RIBBON-1 study (a double-blind placebo-controlled RCT) is downgraded by the omission of 'placebo' in the description of the study and of the therapies assigned to patients. In the lengthy discussion of safety (p 36- 38), the omission of the statement that the comparator arm in RIBBON-1 contained placebo is pejorative to the discussion. The ERG notes that the level of AEs seen in RIBBON-1 is lower than that seen in other, non-placebo controlled studies. The narrative might even seem to suggest some doubt about the safety reporting in the RIBBON-1 study. However the placebo-controlled study design of RIBBON-1 in fact makes this a more robust study than those with which it is compared.	The ERG does highlight that this is a placebo controlled study in its critique (4.2). However, the ERG does accept this is not explicit in the executive summary, which it should have been, and so has amended (p6). Reference to placebo is also added to section 3.3. Finally, the abbreviations have been amended to explicitly state that in the context of the RIBBON-1 trial, CAPE refers to patients who received capecitabine in addition to placebo (p5)

Issue 2 Baseline characteristics of the prior taxane subgroup

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Pages 8-11 and throughout the report

The ERG states that the prior-taxane treated subgroup of RIBBON-1 “appears to be younger and healthier than the ITT population” (page 8, 9) or “appears to be quite different to (sic) the ITT population. In particular younger and healthier” (page 39)</td>
<td>These statements should be amended to say “there appear to be some non-significant differences between the prior taxane subgroup and the ITT population”</td>
<td>The difference in mean age between the prior taxane subgroup (53.4 ± 11.5) and the ITT population (56.6 ± 11.5) is well within the standard deviation of the mean values and so is not significant. Similarly, the percentage difference in ECOG 0 patients (58.8% prior taxane versus 52.7% ITT) is only 6% and so very unlikely to be a significant difference.

Furthermore, the survival for this “younger and healthier” subgroup randomised to the PLACEBO + CAPE arm of the trial is worse than the ITT population (Table 17, p40 of the ERG report).

From Table 17: Comparison of PFS and OS reported for the prior taxane subgroup and for the ITT population in the placebo-capecitabine arm of RIBBON-1
<table>
<tr><th>Endpoint</th><th>Prior taxane subgroup (n=84)</th><th>ITT population (n=206)</th></tr>
<tr><td>PFS events (%)</td><td>63 (75.0%)</td><td>162 (78.6%)</td></tr>
<tr><td>PFS (median, months)</td><td>4.2</td><td>5.7</td></tr>
<tr><td>Number (%) of patients who died</td><td>44 (52.4%)</td><td>99 (48.1%)</td></tr>
<tr><td>OS (median, months)</td><td>20.5</td><td>22.8</td></tr>
<tr><td>OS (median, months) using RPSFT model [a]</td><td>15.0</td><td>-</td></tr>
</table>
[a] Estimate using RPSFT model taken from Table 32 of the MS,</td>
<td>Using statistical tests to compare baseline characteristics is not generally recommended (See, for example, Pocock et al, 2002). The advice is that the emphasis should be on whether or not observed differences are clinically important. In view of these factors the ERG limited their critique to an observation of the data. It should, however, be noted that when considering whether or not the prior taxane subgroup is significantly different, this subgroup should be compared with the population that did not receive a taxane, rather than with the entire ITT population of which it is a part.

Reference:

Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practiceand problems. Stat Med. 2002; 21(19):2917-30.</td>
</tr>
</table>

Issue 3 Proportion of life-years gained in PD

<table>
<tr><th>Description of problem</th><th>Description of proposed amendment</th><th>Justification for amendment</th><th>ERG response</th></tr>
<tr>
<td>Page 9 and elsewhere.

The ERG raised concerns over the proportion of incremental life-years gained spent in PD (approximately 60%) according to the economic model. Indeed, on page 59, they comment that “in view of the limitations of the RPSFT method, such gains may be overly optimistic”.</td>
<td>We request that this statement, and references to this observation, be removed due to lack of recognition of the clinical evidence on which the model is based.</td>
<td>Our submission includes a table (Table 32, p121) demonstrating that the outputs of the model are in agreement with the median PFS and OS gains observed in the trial.
<table>
<tr><th>Outcome</th><th>Clinical trial result</th><th>Model result</th></tr>
<tr><td colspan="3">PLA + Cape</td></tr>
<tr><td>Progression-free survival</td><td>Median = 4.2 months</td><td>Median = 4 months</td></tr>
<tr><td>Post-progression survival</td><td>N/A</td><td>9.79</td></tr>
<tr><td>Overall survival</td><td>Median = 15 months</td><td>Median = 15 months</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="3">BEV + CAPE</td></tr>
<tr><td>Progression-free survival</td><td>Median = 8.7 months</td><td>Median = 8 months</td></tr>
<tr><td>Post-progression survival</td><td>N/A</td><td>N/A</td></tr>
<tr><td>Overall survival</td><td>Median = 24 months</td><td>Median = 23 months</td></tr>
</table>
In both arms, median PFS is approximately one third of total OS.

Even when adjustment for post-progression therapies is ignored, the median proportion of overall time spent by patients in PFS is 20.5% (4.2/20.5 months) for PLA + CAPE and 30.6% (8.7/28.4months) for BEV + CAPE (See table 17 on page 40 of the ERG report).</td>
<td>It has been shown that in trials of first-line chemotherapy for mBC the median OS is typically about three times the median PFS (Kiely et al 2010). The ERG has, therefore, removed statements from the report as requested by the manufacturer.

Reference:
Kiely BE, Soon YY, Tattersall MHN, Stockler MR. How Long Have I Got? Estimating Typical, Best-Case, and Worst-Case Scenarios for Patients Starting First-Line Chemotherapy for Metastatic Breast Cancer: A Systematic Review of Recent Randomized Trials. J Clin Oncol. 2011; 29(4):456-63.</td>
</tr>
</table>

Issue 4 Changes to the baseline characteristics of cohort

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10. The ERG describes the use of a "UK specific cohort" to calculate drug dosages, and subsequently costs, but do not provide a reference or describe the characteristics of the cohort.	The appropriate reference for the "UK specific cohort" and/or details of the relevant characteristics, including weight and body surface area for example, should be provided. Using an external source of patient characteristics in this way should be described as a sensitivity analysis rather than a correction.	The outcomes described in the RIBBON-1 study were achieved by the therapies administered to the patients in the study, according to their particular weight (mean = 72.1kg) and body surface area (mean = 1.517m^2). The economic model uses as much data as possible from the randomised placebo controlled trial, RIBBON-1. This adjustment increases the base case ICER by almost 10% and we cannot verify the validity or accuracy of the revised costs of therapy proposed by the ERG.	A reference has been added.

Issue 5 Utility calculation

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 10. The ERG suggests we have incorrectly used the age of individuals with mBC in our calculation of utility from the regression analysis of Lloyd et al. In fact we have used a mean age of 47 years as recommended by LRiG on p82 of the on-going NICE MTA in mBC (Lapatinib and trastuzumab in combination with an aromatase inhibitor for first-line treatment of metastatic hormone receptor positive breast cancer which over-expresses HER2. Fleeman et al, September 2010, Project number 09/101/01). This is the mean age of respondents to the original general population study conducted by Dolan et al in 1996.	The ERG should justify the change in their methodology from September 2010 and describe this as a sensitivity analysis rather than a correction.	The use of a mean age of 40 years in the utility algorithm described by Lloyd et al increases the base case ICER by more than 10% and is inconsistent with recent appraisals.	The ERG accepts the manufacturer's point and has amended the text in the report and adjusted the revised utility so that it only reflects the typing error in the formula.

Issue 6 Eligibility criteria

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 14. The ERG report states that "clinical advisors believe a lower proportion (of patients) may receive treatment with chemotherapy" since a majority will be ER+ve and treated with endocrine therapy. The ERG therefore suggests the proportion to be 60%, instead of 72% as stated in the submission.	We propose the original proportion of patients receiving chemotherapy remain unchanged at 72%.	Our figure is based on 1st line chemotherapy, rather than any possible therapy and is therefore to be preferred.	The revised estimate was meant for illustrative purposes to show how the number of patients may be altered. However, since the Roche figure is derived from market research data, the ERG is willing to keep the figure at 72% in the table and has amended accordingly.

Issue 7 Off label usage of capecitabine

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 18. The "ERG notes that in clinical practice, while CAPE is only licensed for patients who have 'failed' an anthracycline or a taxane, in clinical practice it is given to patients who are not considered appropriate for an anthracycline or a taxane, regardless of whether they have 'failed' treatment regimens in the past"	Please add the words "in off label usage" to the end of this statement	Roche Products Ltd, as the licence-holder for capecitabine, must try to ensure that any description of off-label use of its product is clearly labelled as such.	Amended as suggested.

Issue 8 Systematic review methodology

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 23. The ERG report states that it is not explicit whether the application of inclusion/exclusion criteria was cross-checked by a second reviewer.	We would like to make it clear that a process similar to that described in the Appendices, Section 9.12.7 and Section 9.13.6 was applied to the systematic review of clinical effectiveness studies described in Section 9.2. We regret any confusion caused by this omission.	N/A	N/A

Issue 9 ERG request for sub-group data

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 39. The ERG states that they "requested additional data on baseline characteristics, post-progression treatment and all other outcomes including AEs" and that we did not supply this data. We have re-visited both sets of clarification questions and cannot find a request for details of the baseline characteristics or AEs suffered by patients in the subgroup.	We request this statement is removed from the report.	The inclusion of this statement does not accurately reflect the ERGs request and is an unfair criticism of our willingness to help the ERG and NICE to understand our submission.	The ERG welcomed Roche's willingness to help the ERG understand their submission. In particular, the ERG welcomed the provision of the Clinical Study Report alongside the manufacturer's submission. A request was however made for additional data for the prior Taxane subgroup regarding baseline characteristics, post-progression treatment and all other outcomes including AEs in the second clarification letter (see appendix below).

Issue 10 Justification for pooling of PD survival from both treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59-62. The ERG proposes that it is "appropriate to apply the same model to PD irrespective of trial arm or whether patients had, or had not, crossed". **This is beyond the scope of this appraisal.** We fundamentally disagree with this approach to answer the study question, which addresses the issue of the use of BEV as a **first line** treatment option for mBC patients. It is wholly inappropriate to model post-progression survival based on data from a cohort of patients containing a significant proportion who are known to have received BEV (for which BEV is not licenced).	Please supplement this analysis and all subsequent references to it with an acknowledgment that the underlying assumption is beyond the scope of the appraisal and implies off-label use of bevacizumab in a second-line setting.	Assuming that a large proportion of patients receive bevacizumab post-progression is not reflective of UK clinical practice and lies outside the marketing authorisation for bevacizumab.	Pooling the data represents an alternative approach to correcting for unlicensed use of BEV. No changes have been made to the report.

Issue 11 ERG pooling of PD survival from both treatment arms

Description of problem	Description of proposed amendment	Justification for amendment	ERG response
Page 59-62. We have identified a significant methodological flaw in the ERG's analysis of post-progression survival. The data points in the Kaplan-Meier analysis of PD survival in all modelled patients presented by the ERG (Figure 6, page 61) differ from those supplied to them in response to clarification question B2a. Most significantly, in the data supplied to the ERG, there were no mortality events between Day 658.972 and Day 806.898 (11 censored events were recorded for this period). However, the chart presented in Figure 6 on page 61 of the ERG report contains a number of data points in this time period.	We request that if the ERG intends to retain this analysis, it must be updated to reflect the data provided to them by Roche.	We suspect that the ERG has misunderstood the content of the product limit survival tables supplied and subsequently incorporated flawed survival data in their amended model.	The ERG acknowledges that there was a problem with the analyses. Revised results are presented in the report.

Appendix: clarification question sent from the ERG to the manufacturer

Question A2 to the second clarification letter was as follows:

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)

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)