Bevacizumab for the treatment of recurrent advanced ovarian cancer
ERRATUM

This report was commissioned by the NIHR HTA Programme as project number 11/40

BMJ Technology Assessment Group

This document contains errata in respect of the ERG report in response to the manufacturer's comments at the second Appraisal Committee meeting.

The table below lists the page to be replaced in the original document and the nature of the change:

Page No.	Change
59	Removal of superscript "b" in the table and corresponding text "HR reported in the manufacturer's submission to be relative to placebo. However, the quoted HR is for placebo relative to bevacizumab."
103	Change of text within the third bullet point, changing "hazard ratio versus bevacizumab" to "hazard ratio versus placebo".

The ERG agrees with the manufacturer that confounding due to post-progression treatment is a well-recognised difficulty associated with interpretation of OS data, but considers that this issue is common to trials evaluating cancer treatments, as highlighted in FDA guidance.[39]

Table 1. Interim analyses of overall survival

OS	Bevacizumab (N = 242)	Placebo (N = 242)
First interim OS analysis[a]		
Number (%) of patients with an event	63 (26.0)	78 (32.2)
Median overall survival (months) (95% CI)	35.5 (30.0 to not estimable)	29.9 (26.4 to not estimable)
HR (relative to placebo) (95% CI)	**0.75 (0.53 to 1.05)**	
Second interim OS analysis[a]		
Number (%) of patients with an event	123 (50.8)	112 (46.3)
Median overall survival (months) (95% CI)	33.3 (29.8 to 35.5)	35.2 (29.9 to 40.3)
HR (relative to placebo) (95% CI)	**1.03 (0.79 to 1.33)**	
Third interim OS analysis[a]		
Number (%) of patients with an event	144 (59.5)	142 (58.7)
Median overall survival (months) (95% CI)	33.4 (30.3 to 35.8)	33.7 (29.3 to 38.7)
HR (relative to placebo) (95% CI)	**0.96 (0.76 to 1.21)**	

[a] First patient was enrolled on 17th April 2007. Cut-off dates for analyses were: first interim analysis = 17th September 2010 (final progression-free survival analysis); second interim analysis = 29th August 2011; and third interim analysis (carried out at the request of the European Medicines Agency) = 30th March 2012.
Abbreviations used in table: CI, confidence interval; HR, hazard ratio; OS, overall survival.

Objective response rate and duration of response

ORR was defined as the occurrence of a complete or partial response, and was confirmed by a repeat assessment performed ≥4 weeks after the criteria for response were first met; criteria for response were assessed based on the modified RECIST criteria (presented in Table 4).

In investigator-assessed ORR, a statistically significant larger proportion of patients achieved an objective response with bevacizumab compared with placebo (190/242 [78.5%] in the bevacizumab group vs 139/242 [57.4%] in the placebo group; p<0.0001); results summarised in Table 12. In addition, the proportion of patients achieving a complete response was larger with bevacizumab (42/242 [17.4%] with bevacizumab vs 22/242 [9.1%] with placebo; statistical significance not reported). The results of the sensitivity analysis for ORR carried out by the IRC are in agreement with the results of the investigator-assessed analysis (summarised in Table 12). The ERG notes that the proportion of patients classified as achieving an objective response is comparable for the investigator-

Competing risks

The manufacturer used PFS data estimated with Kaplan-Meier methodology within the model. However, the ERG notes that death (from any cause) was a competing risk event; competing risks are encountered when patients under study are at risk of more than one mutually exclusive event. By using standard Kaplan-Meier methodology, the manufacturer has not explicitly accounted for competing risks, instead the manufacturer included death from any cause within the definition of PFS; the manufacturer defined PFS as the time from randomisation to disease progression or death due to any cause. However, the ERG believes that due to the low number of death events within the PFS dataset (five within the bevacizumab group and two within the placebo group), standard Kaplan-Meier techniques are likely to have been appropriate for the PFS analysis, and estimates of progression free survival are likely to be reasonable.

Overall survival

OS data were used within the manufacturer's economic model to estimate the proportion of people within the PD health state (PD = OS – PFS) and, implicitly, the death health state (death = 1 – OS) in each model cycle. Similar to the estimation of PFS above, the manufacturer estimated the duration of OS by applying a log-logistic distribution to the Kaplan–Meier OS data from OCEANS. At the time of submission, final OS data were not available (expected in 2013). Therefore, the manufacturer used interim survival analysis carried out in September 2010 to inform the log-logistic distribution. This dataset comprised 35.5 months of data for the bevacizumab group and 33.7 months of data for the placebo group. During these time periods, 29% of patients had died (Section 4.2.1). The probability of survival was then estimated through extrapolation of the chosen distribution and applied weekly for the full time horizon of the model.

The interim analysis of OS carried out in September 2010 was the first of three interim analyses conducted by the manufacturer. The manufacturer also analysed OS at August 2011 and March 2012. The results from these analyses were:

- in September 2010 approximately 29% patients had died; the median OS for bevacizumab was estimated to be 35.5 months compared with 29.9 months in the placebo group (hazard ratio versus placebo 0.751 [0.537 to 1.052])
- in August 2011 approximately 49% patients had died; the median OS for bevacizumab was estimated to be 33.3 months compared with 35.2 months in the placebo group (hazard ratio versus placebo 1.027 [0.792 to 1.331])
- in March 2012 approximately 59% patients had died; the median OS for bevacizumab was estimated to be 33.4 months compared with 33.7 months in the placebo group (hazard ratio versus placebo 0.960 [0.760 to 1.214])

Within the MS, the manufacturer presented the Kaplan–Meier OS plots for the September 2010 and March 2012 interim analyses (Figure 6 and Figure 7, respectively). In Figure 6, the vertical lines indicate 95% CIs. In Figure 7, a line indicates censoring.