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BY E-MAIL

Dear Christopher,

MULTIPLE TECHNOLOGY APPRAISAL – Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma

Thank you very much for sending us the Appraisal Consultation Document (ACD) for the above technology appraisal.

Roche welcomes the provisional clinical findings of the Appraisal Committee in relation to establishing the effectiveness of bevacizumab, recognising its ability to address significant unmet clinical need for patients with renal cell cancer. However, the ACD presently concludes that bevacizumab is not cost effective when based on either Roche's submission or on the analysis performed by the Assessment Group (AG).

Roche would like to request that the Appraisal Committee when reconsidering the ACD, evaluate further and deliberate on several key parameters currently included within the AG's economic model which we believe presently compromise the accuracy and validity of the final base case estimate of the bevacizumab ICER. In this context, we would also point out that the ACD is currently not clear regarding which of the alternative assumptions reported are considered to be most robust by the Appraisal Committee in establishing the base case ICER and we would like to request that these are made explicit to us.

We also present in this response to the ACD what Roche considers to be a more appropriate hazard ratio from the AVOREN trial for use in the AG's model in relation to appropriately taking into account post progression treatments and also present details of the actual dosing observed from the AVOREN trial because we believe the AG's treatment duration assumptions for bevacizumab are inaccurate.

Roche would like to request that if the points raised below are considered valid by the Appraisal Committee that they are incorporated into the AG's economic model cumulatively rather than as part of any univariate analysis in order to report a revised base case ICER for bevacizumab. Alternatively, if any of the points raised are not considered valid then we would like to request that the Committee provide a clear explanation and rationale as to why alternative assumptions are preferred.

1 WHETHER YOU CONSIDER THAT ALL OF THE RELEVANT EVIDENCE HAS BEEN TAKEN INTO ACCOUNT

It is unclear from the ACD as to whether or not Roche's response to the Assessment Group's Report discussing the validity of some of the assumptions used in their analysis was considered by the Committee. There are a number of differences between the clinical and economic analyses performed by Roche and those conducted by the AG which have a very significant impact on the final ICER and therefore it is important that each of these points be considered in turn:

A) Overall survival / post-progression treatment effect

In this section we provide a further analysis of the AVOREN pivotal trial that adjusts overall survival for second-line treatments.

Roche's original submission used an overall survival hazard ratio based on the safety population (HR 0.709) whereas the AG's analysis was based on the ITT population (HR 0.75).

Roche maintain that the safety population is the relevant population to consider in the analysis since this represents the population that actually received at least one dose of the study drug. AVOREN was a double-blinded trial and therefore the reason for a patient not receiving drug would not be related to which arm they had been randomised to. Additionally there is no incremental cost prior to the first dose between the two arms so the likelihood of patients not receiving treatment post randomisation is irrelevant. Hence patients that did not receive the study drug do not contribute to informing the decision problem and merely dilute the average costs and outcomes of the patients that did receive the study drug.

None of the analyses undertaken however account for the confounding effects of second-line treatments. This has previously been summarised in a publication by Tappenden et al *"The central difficulty in interpreting overall survival data from many existing cancer trials concerns the number of patients who crossover to alternative therapies following disease progression or treatment failure."…. "The implication for clinical effectiveness is that outcomes observed within the comparator treatment group may be exaggerated, leading to the underestimation of the incremental treatment benefit, whilst the implication for cost-effectiveness analyses is that the cost of achieving such benefits within the comparator arm will also be underestimated if these are omitted from the model."* (Methodological issues in the economic analysis of cancer treatments, Tappenden 2006)

Roche attempted to address the confounding factor of second-line treatments by including the cost of these treatments in our submission, as observed within the AVOREN trial.

However PenTAG noted in their response to comments on the AG report *"that whilst the published paper includes the statement that "Other neoplastic agents were allowed subsequent to progression or toxicity", we are unaware of any published evidence to suggest that TKIs or temsirolimus were used as second line therapies. We were therefore unable to adjust the IFN baseline overall survival data to reflect the use of second line treatment options."*

Roche interpret PenTag's comments to suggest that if they had had access to the patient level data from the AVOREN trial then they would have attempted to adjust overall survival for second-line therapies. This represents an alternative and credible method of adjusting for the confounding effect of second line therapy. Roche agree that AVOREN, being a multinational trial, does not fully reflect the decision problem in this appraisal and that adjusting for second-line therapies would therefore represent a more fit for purpose analysis.

Re-analysis of the AVOREN trial adjusting for second-line therapies by censoring patients that received novel treatments second-line (bevacizumab, sunitinib and sorafenib), results in an overall survival hazard ratio for bevacizumab of 0.613 (C.I.: 0.464; 0.811) stratified by Motzer score and region and 0.605 (CI: 0.459; 0.796) un-stratified.

There is an inevitable trade off between maintaining randomisation of the resulting cohort versus how well it represents the decision problem of interest. The validity of the revised hazard ratio relies on the assumption that the characteristics of the censored patients are balanced between the arms and are representative of the patient population as a whole. It can be seen from Table 1 below that the baseline characteristics of the censored patients are broadly similar to the ITT population except possibly with regards to Motzer score. The hazard ratio stratified by Motzer score and region takes into account any imbalance between the arms relating to Motzer score and therefore is the most applicable estimate to use.

Table 1: Baseline characteristics of censored patients

	Censored Population		ITT Population	
	Bevacizumab + IFN	INF	Bevacizumab + IFN	IFN
Number of patients	91	56	325	316
Male	67%	82%	68%	73%
Motzer score— Favourable Intermediate Poor	 31% 62% 8%	 46% 54% 0%	 30% 61% 9%	 32% 60% 8%
Age <65	67%	56%	63%	63%
No. of metastatic sites	2.34	2.52	2.41	2.39
Karnofsky Score				

100	57%	52%	44%	38%
90	25%	34%	31%	39%
85	1%	0%	1%	0%
80	12%	11%	17%	16%
75	0%	0%	0%	0%
70	4%	4%	6%	7%
Mean Weight	76.63	79.85	76.03	77.39

Second-line treatments reported in Roche's original submission were based on a table in the AVOREN clinical study report entitled "Summary of subsequent antineoplastic therapy started after disease progression by trial treatment". In the course of estimating a revised hazard ratio it was discovered that this post-progression treatment table does not include any bevacizumab administered post-progression (off licence second-line use) in the bevacizumab+IFN arm. This was because any treatment with bevacizumab had been started prior to disease progression and did not meet the definition of treatments within this specific table. This has been corrected in the re-analysis so that all second-line novel agents are censored.

Roche therefore requests that any analysis relating to bevacizumab should now use the overall survival hazard ratio of 0.613 as we believe this best reflects the treatment benefit of bevacizumab within its UK licensed indication, compared with a scenario and consequent outcomes where it is not made available (i.e, the decision problem of interest).

Analysis utilizing the ITT hazard ratio would in effect be modeling the outcomes of bevacizumab followed by a bundle of other novel agents (many off license and unlikely to be prescribed within the UK NHS) compared to IFN followed by a bundle of novel agents.

B) Average cumulative dose administered per patient

For patients who received bevacizumab there is presently a discrepancy between the cumulative dose recorded in the AVOREN trial and that estimated by the AG. This results in a cost difference between the two models of £12,535 (and an approximate difference in the ICER we estimate of approximately £47,000).

Roche used the actual mean cumulative dose as observed in the AVOREN trial to calculate drug acquisition cost. We consider this the optimal method of calculating drug acquisition costs as it is a precise reflection of drug consumption that resulted in the health benefits observed in the trial.

The AG used an estimated average cumulative dose based on the assumption of treatment until progression and an average dose intensity taken from the Escudier *et al* 2007 paper.

As can be seen in Table 2 below, the AG have also overestimated the treatment duration of first-line bevacizumab by approximately 70% and hence the drug acquisition cost is also vastly overestimated.

Table 2: Drug dosage - Bevacizumab and IFN alfa-2a in both study arms (safety population) as per protocol

	Bevacizumab + Interferon alfa-2a			
	Bevacizumab (Clinical trial)	**Interferon alfa-2a (Clinical trial)**	**Bevacizumab (Assessment Group Estimate)**	**Interferon alfa-2a (Assessment Group Estimate)**
Average No. of Administrations	15.51	84.59		
Average Treatment duration (months)	7.36	6.48	12.0	12.0
Average Dose (mg) per Administration	756.7	7.89	88% dose intensity for 12.0 months	83% dose intensity for 12.0 months
Mean Total Dose (mg)	11,733.43	667.55		
Mean drug costs per patient (Present value using standard 3.5% discount rate)	£26,627	£3,505	Not split out in modeling	Not split out in modeling
	£30,132		£42,667	

Roche would like to request that a re-analysis of the economic model is performed for bevacizumab to include the costs based on the average cumulative dose as observed in the AVOREN trial itself. (We note that the clinical outcomes of bevacizumab at the dose assumed by the AG are unknown).

C) Administration costs (number of administrations)

As per point B above regarding the assumed dose administered, the AG assumed treatment until progression at the per protocol treatment frequency when estimating the number of administrations provided.

The number of administrations of IFN and bevacizumab as observed in the AVOREN trial were considerably less than those estimated by the AG as the average treatment duration was only 7.36 months compared to 12 months assumed by the AG. Additionally on average, bevacizumab administrations actually occurred every 16.5 days as opposed to the per protocol cycle length of every 14 days, further contributing to the present overestimate.

Roche would like to request that a re-analysis of the economic model is performed for bevacizumab to include the costs based on the actual number of administration observed in the pivotal trial.

D) Administration costs (cost per administration)

The administration of bevacizumab is more rapid than for chemotherapy regimens and as such applying the cost of an average chemotherapy administration (£189 in 2006/7 reference costs (HRG code SB15Z), uprated to £197 for 2007/8 by the Assessment Group) places an inappropriately high cost on the administration of bevacizumab. Roche suggests that it would be more appropriate to consider the lower interquartile range figure for the relevant reference cost (£95 in 2006/7 reference costs, uprated to £98 for 2007/8). This is appropriate given the average administration time of bevacizumab of approximately 30 minutes (from the second administration) compared to commonly administered agents such as irinotecan, leucovorin, and other combination therapies which take an average of two hours to infuse (see relevant Summaries of Product Characteristics). Applying this more appropriate administration cost would further reduce the treatment cost of bevacizumab + IFN whilst ignoring this we believe biases the results against bevacizumab + IFN.

Conclusion

Roche believes that the cumulative impact of all of these model parameter refinements upon the final ICER of bevacizumab is highly significant. However, it has not been possible for us to estimate a revised ICER ourselves as we only have access to the "read-only" version of the AG's Economic Model which has limited our ability to understand the impact of these changes and to respond fully to this consultation.

We would therefore like to request that the AG's economic model is re-run with our proposed revised assumptions and that the results are shared in a fully transparent manner, along with details of all of the final assumptions relied upon by the Committee in determining a revised base case ICER which can subsequently be used as the basis for continued engagement and dialogue going forwards.

2 WHETHER YOU CONSIDER THAT THE SUMMARIES OF CLINICAL AND COST EFFECTIVENESS ARE REASONABLE INTERPRETATIONS OF THE EVIDENCE AND THAT THE PRELIMINARY VIEWS ON THE RESOURCE IMPACT AND IMPLICATIONS FOR THE NHS ARE APPROPRIATE

Please refer to our response to question 1 above.

3 WHETHER YOU CONSIDER THAT THE PROVISIONAL RECOMMENDATIONS OF THE APPRAISAL COMMITTEE ARE SOUND AND CONSTITUTE A SUITABLE BASIS FOR THE PREPARATION OF GUIDANCE TO THE NHS

Roche would like to request that the issues raised in response to question 1 are addressed by the Appraisal Committee and appropriate changes incorporated into a re-analysis of the baseline ICER of bevacizumab which is shared transparently with stakeholders.

Roche would also like to point out that for this particular appraisal of bevacizumab in renal cell cancer we believe that other relevant factors (such as those listed in Section 6 of the revised Guide to Methods) should be explicitly taken into account by the Appraisal Committee. These factors include “severity of disease” and the “degree of clinical need of patients with the disease”. We would like to request that the position of the Appraisal Committee is made clear and transparent in relation to whether and how these factors have been considered when interpreting the final ICER for bevacizumab.

4 ARE THERE ANY EQUALITY RELATED ISSUES THAT NEED SPECIAL CONSIDERATION THAT ARE NOT COVERED IN THE ACD?

We believe there are none.

We hope that these comments are helpful to the Appraisal Committee.

Yours sincerely,