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BY E-MAIL

Dear Chris,

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

Thank you for the opportunity to comment on the additional evidence provided in relation to the above technology appraisal. Our comments on both the new evidence and the DSU analysis of Roche's economic modelling assumptions are provided below in three sections.

There were some areas of Roche's ACD response that remained unclear to the DSU and for which clarification is therefore required. These areas are addressed in section 1 of this response.

In section 2 we provide feedback on two key economic modelling assumptions which Roche believes are presently incorrect in the current Assessment Group's (AG) economic model and have a large impact on the base case ICER. These assumptions are:

1. The mean number of treatments, which impact:
    a. The expected cost of drug acquisition
    b. The expected administration costs
2. Estimate of the overall survival benefit.

The handling of these assumptions raises generic methodology issues when evaluating the cost effectiveness of metastatic oncology medicines and requires further discussion as no clear consensus on best practice currently exists. Further analyses have been generated to help inform the methodological issues and any potential amendment of the Assessment Group's economic model.

Finally, we have reviewed the new end-of-life criteria for certain medicines being proposed by NICE where fulfillment of these criteria might permit access to a higher cost/QALY approval threshold and believe that this appraisal of Avastin in renal cell cancer would qualify for such consideration. We have therefore included in section 3, our evaluation of Avastin in renal cell cancer against the proposed criteria.

1 POINTS OF CLARIFICATION

In this section we attempt to address issues raised by the DSU in their commentary on the Roche ACD response. In addition we wish to clarify how the overall survival analysis included as part of our ACD response was performed, as some of the terminology used appears to have led to the misinterpretation of results.

1.1 Trial Population Definitions

In response to the comments by the DSU we wish to clarify the definitions of the populations used in the analyses of the AVOREN trial presented to date.

Population	IFN + Placebo	IFN + bevacizumab
ITT population used in AG analysis	322 patients	327 patients
Patients who withdrew prior to treatment commencing	6 patients	2 patients
Population used in Roche's response to ACD	316 (322-6)	325 (327-2)
Patients where placebo was administered in bevacizumab arm and bevacizumab administered in placebo arm	11 (11 doses in total)	4 (6 doses in total)
Safety population used in Roche's original submission where patients which mistakenly received a dose of bevacizumab were analysed as being in the placebo arm	305 (316-11)	336 (325+11)

Roche's original submission was based on the "Safety" population, defined as patients who had one or more doses of bevacizumab being analysed as part of the bevacizumab arm of the trial. The costs and treatment benefits of the 11 patients who received one dose of bevacizumab 'in error' were included in the bevacizumab arm and

removed from the placebo arm. Patients who withdrew prior to treatment were also excluded in the original analysis as no bevacizumab or placebo was administered. Roche considered this would produce a more appropriate estimate of the treatment effect of bevacizumab given the decision problem of interest.

1.2 Dose Intensity Quoted in AVOREN Study Paper (Escudier et al. 2007)

Currently the AGs base case analysis assumes that treatment is given until disease progression which overestimates the cost of drug administration as some patients stopped treatment prior to disease progression. The Assessment Group indicated this assumption was made based on the study publication.

For the purpose of clarification, the study paper referred to by the DSU quotes a mean dose intensity of 88% for Avastin which was calculated as follows:

$$\frac{\text{Observed cumulative dose}}{\text{Expected dose if given as per protocol for the observed treatment duration}}.$$

This calculation accounts for the following:

- Treatments missed or delayed
- Dose reduction per treatment.

This method however does not account for treatment cessation prior to progression. Additionally some patients were treated beyond progression with bevacizumab and this period was included in calculating the 88%.

When considering the DSU comments in relation to Roche potentially underestimating drug cost based upon censoring, an error in the methodology for calculating the expected mean dose from the patient level data has been identified by us. Roche would like to apologise for any confusion this error has caused. We will clarify and correct for this in section 2 below.

However as outlined in further detail in section 2, Roche still believes that the current AG assumptions relating to drug administration and costs are over-estimated.

1.3 Roche ACD Overall Survival Analysis

As part of our response to the ACD we presented overall survival results based on censoring patients that had received systemic post-protocol treatments that are not available in the UK. The analysis within the ACD response was based on the ITT population less patients that withdrew prior to commencing treatment.

Unlike the analysis performed by Pfizer, not all patients that received post-protocol treatments were censored, only those that had received systemic post-protocol treatments not available in the UK. Furthermore, censoring of patients occurred only at the point of progression and not at the point of randomisation.

56 and 91 patients in the bevacizumab and placebo arms respectively had received post-protocol systemic treatments and thus were censored at the time of progression.

Table 1 (Baseline characteristics of censored patients) of Roche's ACD response appears to have been misinterpreted, as the DSU describes this population as patients that had not received post-protocol treatments. In fact, this population did receive post-protocol systemic treatments. Therefore to clarify, all patients were included to inform the PFS analysis and 269 patients (325 minus 56) contributed towards post-progression survival in the bevacizumab arm and 225 patients (316 minus 91) contributed towards post-progression survival in the placebo arm.

Please see below the revised table displaying the data that the DSU assumed they were reviewing. As can be seen, the baseline characteristics remain broadly similar between arms.

Baseline characteristics of no-post-protocol systemic therapies patients

	no-post-protocol systemic treatment population		**ITT Population less withdrawals prior to commencing treatment**	
	Bevacizumab + IFN	INF	Bevacizumab + IFN	IFN
Number of patients	236	266	325	316
Male	68%	71%	68%	73%
Motzer score— **Favourable** **Intermediate** **Poor**	 30% 61% 9%	 29% 61% 10%	 30% 61% 9%	 32% 60% 8%
Age <65	61%	65%	63%	63%
No. of metastatic sites	2.44	2.36	2.41	2.39
Karnofsky Score				
100	39%	35%	44%	38%
90	33%	40%	31%	39%
85	1%	0%	1%	0%
80	19%	17%	17%	16%
75	0%	0%	0%	0%
70	7%	8%	6%	7%
Mean Weight	75.80	76.86	76.03	77.39

2 RECOMMENDED AMENDMENTS TO THE AG ECONOMIC MODEL

Roche is still of the firm opinion that to derive a true estimate of the "treatment effect" of bevacizumab for the purpose of informing cost effectiveness, in this particular situation we consider the safety population and not the ITT population to be most appropriate. The reasons to support this have been previously set out in our responses to the AG Report and the ACD and are discussed further in section 2.1 below.

Given there is still uncertainty as to which population is most appropriate, we have investigated the effect of changes to assumptions based on the ITT population. Using the ITT population is a conservative approach as use of the safety population produces a lower ICER.

Below we present alternative methods for estimating bevacizumab drug acquisition and administration costs which we believe better reflect the evidence base. Additionally, we have further explored the effects of censoring post-protocol systemic therapy when estimating overall survival to reflect the decision problem.

2.1 Appropriateness of basing the analysis on the safety population

The DSU suggest that including patients in the analysis that withdrew before treatment began allows modelling of compliance (p. 43-44). It is unclear how including patients who did not start any therapy helps inform the decision problem and the estimate of the treatment effect of bevacizumab. Given there is no incremental cost between the two arms prior to treatment commencing, patients did not know which treatment they would receive and the outcomes of withdrawal are unknown, the rationale for including these patients as it reflects compliance does not appear a valid justification.

The outcomes of patients that 'mistakenly' received a dose of bevacizumab in the placebo arm are not generalisable to clinical practice as these errors were due to the double-blind nature of the trial. The inclusion of these patients therefore confounds the results of estimating the treatment effect of bevacizumab. The rational for censoring these patients is comparable to that of censoring patients who received post-protocol treatments not available in the UK in that we are attempting to adjust the trial results to best reflect the decision problem of interest.

The risk of including these patients in the bevacizumab arm or censoring them at the point of error is that this might inadvertently create imbalance between the baseline characteristics of the arms of the trial and break randomisation. It is highly likely that including these patients in the analysis will bias the results due to the mistaken use of the wrong drug, whereas it is less certain that baseline characteristics will become less well balanced using the safety population vs the ITT.

In summary, censoring patients who received the incorrect intervention or no intervention may indeed compromise randomisation by patient characteristics. However it is equally important for the Appraisal Committee to acknowledge that using the ITT population without such censoring clearly breaks randomisation within the trial according to allocated treatment. Therefore a choice has to be made on the trade-off of preserving randomisation of allocated treatments or randomisation of patient characteristics.

The specified decision problem is to evaluate the clinical and cost effectiveness of bevacizumab followed by best supportive care compared to no treatment followed by best supportive care. Roche would argue that preserving the randomisation of the allocated treatments is preferable to preserving randomisation of patient characteristics. Failure to do this could result in evaluating the clinical and cost effectiveness of a treatment strategy which is inconsistent with both the decision problem of interest and likely NHS practice.

2.2 Estimated mean number of treatments and cumulative dose

The DSU commented that censoring within the trial would cause the mean observed dose to be an under estimate of the expected dose. This was based on the fact that not all patients had progressed at the point of un-blinding However a large proportion of patients had completed treatment by the point of un-blinding, hence we assumed the dosing data was sufficiently complete to provide a reliable estimate of the expected dose. We acknowledge though that due to censoring of some patients prior to completion of treatment this may underestimate the expected dose.

However as acknowledged by the DSU, given the definition of the dose intensity figure of 88% quoted in the study paper (see section 1.2) the current AG model will be overestimating drug acquisition cost.

As mentioned in section 1.2 above as a result of investigating how to best account for censoring of patients prior to treatment cessation we discovered that some patients had continued on bevacizumab post progression (off-licence). These doses were captured in the 88% included in the study paper but not in our original economic submission. Recalculating dose intensity as defined by the study paper but only including treatment up until progression is 92%.

We have attempted to address the issue of patients being censored prior to completing treatment by using survival analysis modelling on time until treatment cessation to extrapolate the treatment duration to account for missing data. This is consistent with the methodology used in both the AG and Roche model for estimating time to progression. To remain consistent with the AG model we performed this analysis over a 10 year time horizon.

Presented in the table below are the results based on the area under the curve of the above analysis.

Estimated Administrations and Dose

	Bevacizumab + Interferon alfa-2a			Interferon alfa-2a		
Study Medication	IFN-2a	Bevacizumab	Placebo	Bevacizumab	IFN-2a	Placebo
Nr. of Patients (ITT)	327	327	4	11	322	322
Mean observed Dose per Administration	7.88	756.87	704.67	699.27	8.18	767.93

Drug Administration

The DSU agreed that the cost currently applied to a bevacizumab administration visit in the AGs model appeared high. They also pointed out that the Appraisal Committee had agreed, when appraising erlotinib, that a one hour docetaxel infusion should be assumed to cost £170. We have therefore assumed the same administration cost in this analysis.

Drug Costs

The drug cost per patient was calculated as the present value (based on a 3.5% discount rate) of the expected mean number of treatments multiplied by the mg per treatment and cost per mg of £2.31.

The dose intensity figure of 92% includes dose delays and dose reductions. Actual dose per administration divided by expected does per administration was 99% (756.9/760) therefore we estimate the cycles per month to be 92.4% (the expected cycles per month per protocol * 88%/99%) that of the protocol dosing schedule.

Shown in the table below is the drug acquisition and administration costs based on the above proposed methodology.
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Expected mean Drug acquisition cost and cost of administration

	Bevacizumab + Interferon alfa-2a Arm
	Bevacizumab (Roche revised estimate)
Average No. of Administrations	18.06
Average Treatment duration (months)	9.02
Mean Total Dose (mg)	13,672
Mean drug costs per patient*	£30,975
Mean drug acquisition cost of bevacizumab when applying 10g cap*	£22,077
Mean administration costs per patient*	£3,012

*** Present Value at a discount rate of 3.5%**
Attached as an appendix is the workbook used to calculated the figures presented above.

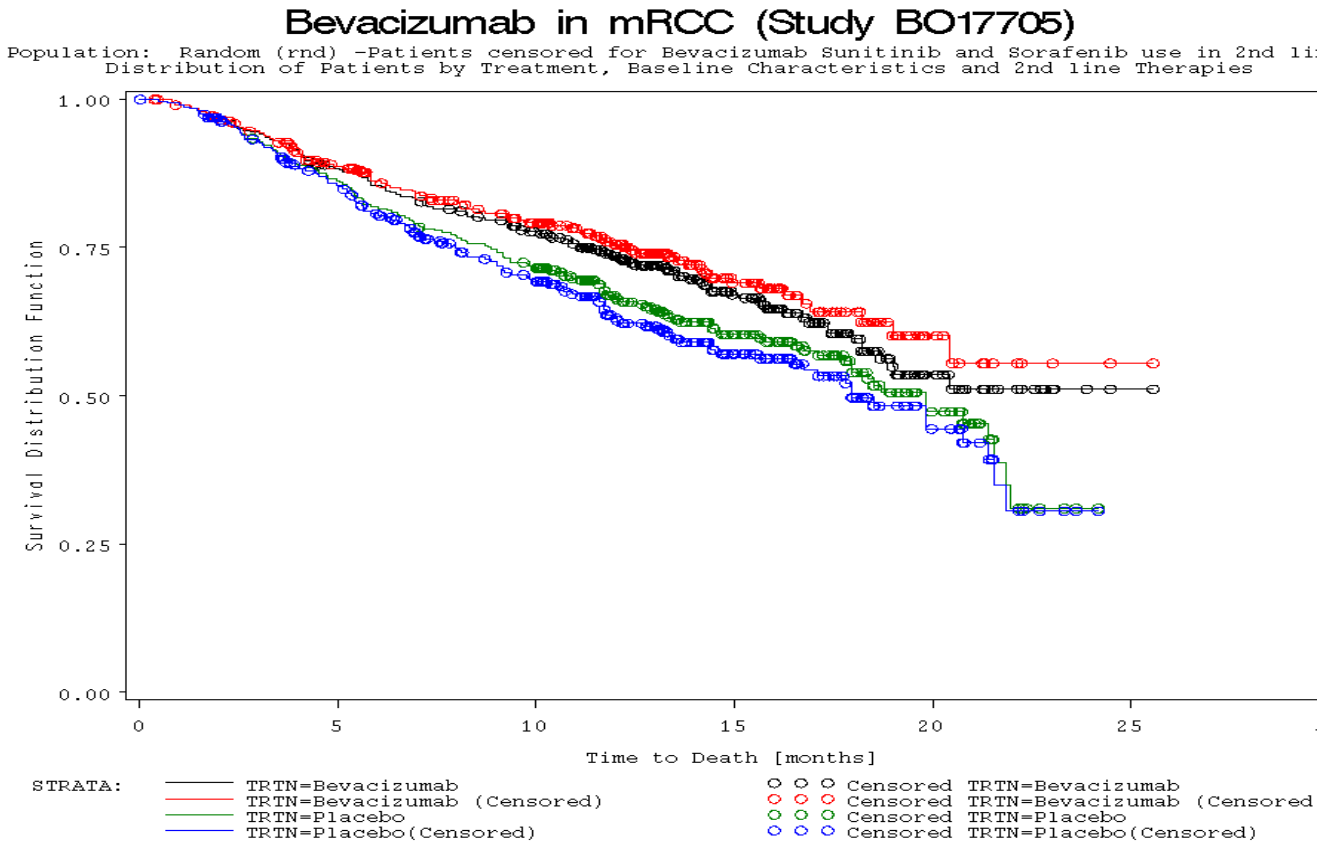
2.3 Estimate of Overall Survival

An additional analysis was performed using the same methodology recommended by the Appraisal Committee to estimate the overall survival incremental benefit of sunitinib over IFN. As highlighted earlier this is a conservative approach compared to using the safety population.

The analysis is similar to that presented in the ACD response but used the full ITT population (649 patients) but includes all patient randomised including those that withdrew before treatment began.

Figure 1 below shows the Kaplan-Meier overall survival curves of the ITT population when censoring for post-protocol systemic treatments compared to the ITT Kaplan-Meier curves when no censoring for post-protocol treatments.

Figure 1: Overall Survival based on the ITT population (649 patients including patient who withdrew prior to treatment)



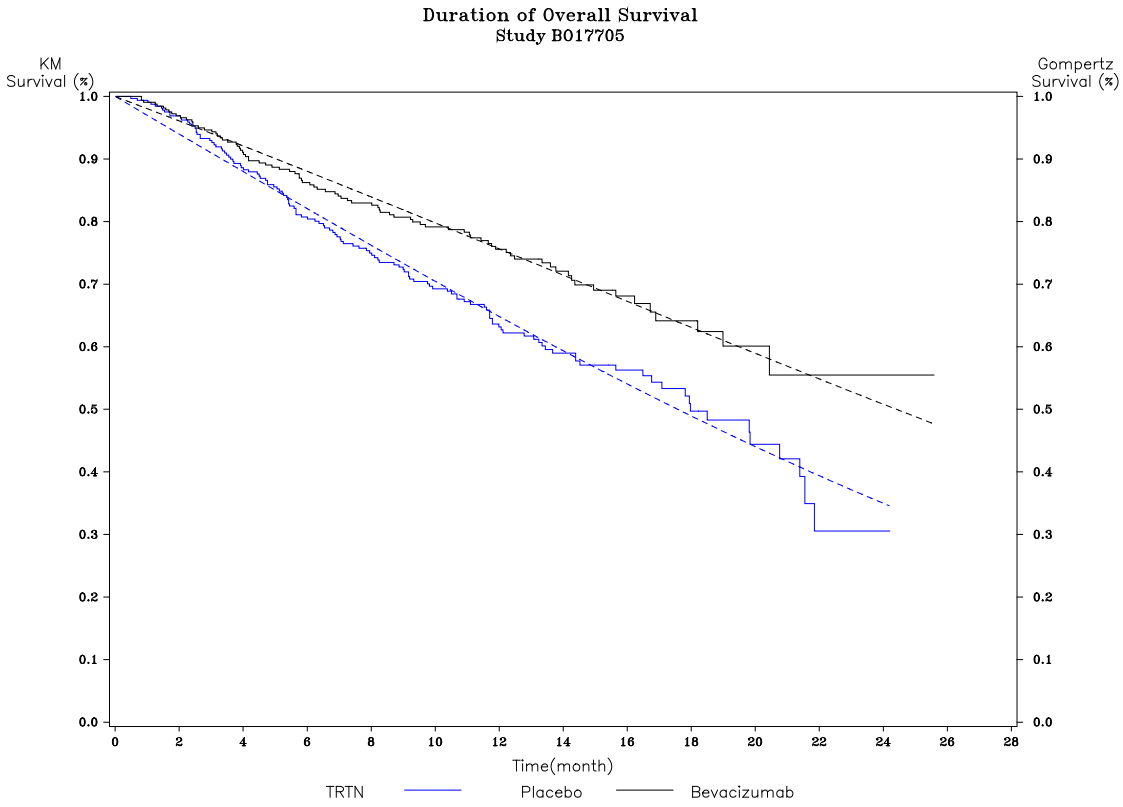
As can be seen, censoring of patients results in the risk of death in the placebo arm increasing beyond that seen in the ITT analysis.

The results are consistent with those of the re-analysis presented by Pfizer in that the risk of death increases with censoring in the placebo arm and reduces in the active arm compared to the ITT analysis.

The hypothesis for the risk of death increasing in the placebo arm is that the systemic post-protocol therapies not routinely administered in the UK had a beneficial effect in this arm that is removed when censoring.

Surprisingly the IFN arm still performs considerably better than expected given the results of previous randomised studies. Also the effect of censoring the post-protocol systemic therapies does not appear to have had as marked an effect as was shown in Pfizer's reanalysis of the A6181034 trial. This difference is potentially due to the different methodology applied; we have only censored patients that received post-protocol systemic treatments, not all patients that had any post-protocol treatment.

A Gompertz function was used to extrapolate the overall survival data from the reanalysis following censoring as it resulted in the best statistical fit (see appendix A)



Source: SAS v8.2 aultmanr $HOME/cdp10044.pbe/i17705b.pbe/rndbss.sas 21NOV2008 15:43

The table below reports the results of extrapolating the Gompertz functions (shown above) over a 10 year time horizon.

ITT population censoring post-protocol systemic treatments

	Re-analysis (censoring both arms)
Mean Overall survival Placebo (months)	19.95
Mean Overall survival Bev (months)	26.55

Attached to our response are two Excel Workbooks containing the Gompertz functions and the formulae used to calculate the mean OS for each arm (Appendices B and C).

Please do not hesitate to contact us if you require any assistance with using these Workbooks.

3 PROPOSED CHANGES TO THE WAY "END OF LIFE" TREATMENTS ARE APPRAISED BY NICE AND IMPLICATIONS FOR BEVACIZUMAB FOR THE TREATMENT OF mRCC

We have assessed bevacizumab + IFN for the treatment of mRCC in the context of each of the proposed 'end-of-life' criteria recently proposed by NICE for recommending life-extending medicines where the most plausible ICER is greater than £30,000.

- **Licenced patient population**: The number of new mRCC patients diagnosed each year that would be eligible for treatment with bevacizumab+IFN is approximately 1,800, which is less than the proposed 7,000 new patients per annum representing the present upper bound proposal

- **Life expectancy**: Bevacizumab+IFN is indicated for the treatment of patients with advanced and/or metastatic RCC, a terminal illness whereby patients are not, on average, expected to live for more than 24 months. In terms of the current NHS standard of care, randomised trials have shown that interferon alone results in a median overall survival of approximately 13 months.

- **Substantial extension to life**: Survival estimates based upon the available evidence suggest that the combination of bevacizumab+IFN provides a substantial extension to mRCC patient's lives compared to the current NHS standard of care. Bevacizumab+IFN has demonstrated a clinically meaningful extension in median progression free survival from 5.4 to 10.2 months, almost doubling the time patients remain progression free on IFN (HR= 0.63, 95% CI 0·52–0·75; p=0·0001). Whilst the overall survival data was immature, an unstratified ITT analysis suggested a non-significant benefit in favour of bevacizumab+IFN (HR = 0·79, 95% CI 0·62–1·02; unstratified log-rank test p=0·0670). Furthermore, a pre-planned exploratory ITT analysis of OS stratified by MSKCC risk group and region was similar to the unstratified analysis, with a non-significant improvement in favour of the bevacizumab+IFN group (HR = 0•75, 0•58–0•97;p=0•0267, greater than the pre-specified limit of p<0.0056). Based on the analysis of the ITT population stratified by MSKCC risk group and region, the Assessment Group also estimated that the mean incremental life time gain was 4.07 months.

  It is also important to note that there was significant use of post-progression treatments documented in the AVOREN study, which are not currently available in the UK. Therefore, it is expected that the incremental OS improvement over standard of care in the UK would exceed that observed in the AVOREN study, as the post protocol treatments may have confounded the treatment effect of adding bevacizumab to IFN. Based on the stratified ITT population and censoring for post protocol systemic treatments, it is estimated that the addition of bevacizumab to IFN offers 6.04 months extension of life.

- **Alternative treatments**: No alternative treatment with comparable benefits are currently available on the NHS.

Given the above we would conclude that Avastin for use in renal cell cancer should now qualify for appraisal against a higher cost/QALY threshold level as presently proposed for end-of-life medicines.

Please do not hesitate to contact us if we can provide any further clarification of our response.

Yours sincerely.

APPENDIX A

Statistical fit for no-post-protocol systemic treatment parametric functions

MODELTYP	PARAM	BIC	AIC	BESTFIT
Gompertz	OS	972.08867639	958.66237824	GOMPERTZ
lnormal	OS	1147.1904073	1133.7641091	
gamma	OS	1153.5017913	1135.6000604	
llogistic	OS	1151.4852373	1138.0589391	
weibull	OS	1159.8524145	1141.9506836	
exponential	OS	1158.6678988	1149.7170334	