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BY E-MAIL

Dear Christopher,

Technology assessment report: Bevacizumab, sorafenib, sunitinib and temsirolimus for renal cell carcinoma

Thank you for the opportunity to review and comment on the technology assessment report.

Please find below our comments on the analysis performed by the assessment group. We have raised a number of points for consideration by the appraisal committee which we feel requires further discussion at the appraisal committee meeting.

Best wishes.

Yours sincerely,

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Points for consideration

There are a number of differences between the clinical and economic analyses submitted by Roche and that conducted by the assessment group. We believe that this compromises the accuracy of the cost effectiveness estimates reported within the HTA assessment report and as such it is critical that the Appraisal Committee is aware of areas where Roche considers the assessment group's interpretation of the evidence is incorrect. Points 1 – 6 describe model parameters where the assessment group have used different assumptions to Roche, while points 7 – 8 deal with more qualitative aspects of the review.

1. Dose Intensity

One key area in which the assessment group has used incorrect data is with regards to dose intensity. Roche acknowledge that the assessment group have used data from the Escudier et al 2007 paper for this parameter, but the explanation of what the data referred to may have misled the group. The specific paragraph of the Escudier et al paper states:

"The median duration of bevacizumab treatment in the bevacizumab plus interferon alfa group was almost twice as long as that of placebo treatment in the control group (9·7 [range 0–24·4] months vs 5·1 [0–24·0] months). Similarly, the median duration of interferon alfa treatment in the bevacizumab plus interferon alfa group was longer than that in the control group (7·8 [0–13·9] months vs 4·6 [0·2–12·6] months). Median bevacizumab/placebo dose intensity was 92% (range 24–122; mean 88%) in the bevacizumab plus interferon alfa group and 96% (39–110; 91%) in the control group; the median dose intensity for interferon alfa was 91% (4–150; 83%) in the bevacizumab plus interferon alfa group and 96% (28–120; 89%) in the control group. " (pg 2106)

The assessment group therefore applied dose intensities of 88%, 83% and 89% to the bevacizumab, IFN (bevacizumab arm) and IFN (control arm) in their economic models. However because the protocol of the trial was that treatment should continue until disease progression, the assessment group applied these figures for the entire duration of PFS in their model. However, both these figures and the median dose intensity figures stated in the original Roche submission are only applicable for the treatment duration observed in the trial. For example, during treatment the mean dose intensity for bevacizumab was 88%, but treatment duration was substantially shorter than time spent in PFS. Hence applying the 88% dose intensity to the entire time spent in PFS will vastly overestimate drug costs.

The overestimation of drug costs by the assessment group can be clearly demonstrated by consideration of the modeling results. Table 44 of the assessment report shows that the PenTAG model estimates a treatment duration of 12.0 months for bevacizumab + IFN. The 88% dose intensity for bevacizumab and 83% dose intensity for IFN are applied to this treatment duration. However clearly when the median treatment duration in the clinical trial was 9.7 months (mean 7.13 for the safety population) for bevacizumab and 7.8 months (mean 6.48 months for the safety population) for IFN (in the bevacizumab arm)

estimating such a high dose intensity for a 12.0 month period will vastly overestimate treatment costs. PFS was substantially longer than time on treatment and therefore the dose rate has to be adjusted so as to model the dose that was actually given in the trial. Assuming an 88% dose intensity for the entire duration of PFS vastly overestimates treatment costs, substantially increasing the ICER for bevacizumab plus IFN. In essence, the Roche economic model calculates the mean cost of bevacizumab and IFN actually used in the clinical trial during PFS, whereas the assessment group's model does not.

The assessment group also states that Roche did not include the dosing data used within the economic model in our written submission. However this data was presented on pages 66-67 of the Roche submission. Data is partially re-represented here for ease of reference, with additional columns showing the drug usage assumed by the assessment group. This data represents the actual doses of the drugs used as first line treatment in the pivotal trial. This illustrates that the drug usage and therefore costs in the trial were much less than assumed by the assessment group. Also apparent is that mean treatment duration was less than median treatment duration. This is expected in this disease area where more patients are likely to have less rather than more treatment than the median due to early disease progression and treatment toxicity in some patients.

Table 1: Drug dosage - Bevacizumab and IFN alfa-2a in both study arms (safety population) as per protocol

	Bevacizumab + Interferon alfa-2a				**Interferon alfa-2a**	
	Bevacizumab (Clinical trial)	**Interferon alfa-2a (Clinical trial)**	**Bevacizumab (Assessment Group Estimate)**	**Interferon alfa-2a (Assessment Group Estimate)**	**Clinical Trial**	**Assessment Group Estimate**
Nr. Of Patients	336	337			302	
Nr. Of Administrations	5,210	28,506			20,027	
Average Nr. of Administrations	15.51	84.59			66,31	
Average Nr. of Administration Months	7.13	6.48	12.0	12.0	5.08	6.0
Total Cumulative Dose (mg)	3,942,432	224,964			163,875	
Average Dose (mg) per Administration	756.7	7.89	88% dose intensity for 12.0 months	83% dose intensity for 12.0 months	8.18	89% dose intensity for 6.0 months
Mean Total Dose (mg)	11,733.43	667.55			542.63	
Mean drug costs per patient (from economic modeling)	£26,627	£3,505	Not split out in modeling	Not split out in modeling	£2,800	£2,952
	£30,132		£42,667			

The assessment group stated that they were concerned with the way drug costs were calculated in the economic model. The above analysis illustrates that the drug costs calculated by Roche were the correct costs to include in the model, whereas those estimated by the assessment group were a significant overestimate. Roche suggest that this will have a very large effect on the base case ICER calculated by the assessment group and request that any analysis relating to bevacizumab should be corrected to include the correct drug costs. Roche estimate that this would reduce the assessment group's base case ICER for bevacizumab + IFN versus IFN from £171,301 to £124,040.

2. Sunitinib Hazard Ratio (HR) data and dose intensity data

Roche believe that the indirect comparison of bevacizumab + IFN and sunitinib is incorrect because it is based on inappropriate hazard ratios. First, Roche advocate the use of the 'safety' population data for bevacizumab + IFN, according to our arguments in point 4 below. Second, Roche believe that the hazard ratios used for sunitinib are inappropriate because they do not represent the most recent data. For Sunitinib PFS a hazard ratio of 0.42 is used by the assessment group, and for OS a hazard ratio of 0.65 is used. However in more recent analyses of the sunitnib trial these hazard ratios have both increased in value, indicating a reduction in efficacy compared to the HR utilised within the assessment report..

The original PFS data considered by the assessment group had a data cut-off of November 2005 (Motzer et al 2007a) but new data is now available that has a data cut-off of February 2007 (Motzer et al 2007b). The new data shows a PFS hazard ratio of 0.52 (0.44 – 0.62) in the investigator-led analysis, and 0.54 (0.44 – 0.66) in the central review analysis. In the recent Cochrane review it is this 0.54 hazard ratio that is quoted, again suggesting that this is the most relevant for consideration in an analysis of the efficacy of sunitinib (Coppin et al 2008).

In addition, data recently presented at ASCO (Figlin et al, 2008; abstract and presentation), shows that the ITT unstratified patient population demonstrates an OS hazard ratio of 0.821. An exploratory no second line treatment patient population showed a hazard ratio of 0.647. It is this figure which is most similar to the 0.65 stated in the Motzer et al 2007a paper and used in the assessment group's report but it is not appropriate to compare this figure with the bevacizumab data. This Hazard Ratio is derived from a retrospective sub-group analysis rather than the primary endpoint analysis of the ITT population, and overall survival was assessed in a sub-group of patients that did not receive second line therapy. Presumably the justification for using this analysis was removal of potential confounding effects of second and subsequent lines of therapy, thus providing a measure of the direct effects of sunitinib or BSC on survival. However, this analysis is flawed for a number of reasons:

- Retrospective analysis of non-predefined subgroups is potentially fraught with bias. No comparisons of demographic data for the sub-group versus the overall population were presented at ASCO, and therefore it is not possible to assess whether this sub-group is representative of treatment naive sunitinib eligible mRCC patients. These patient sub-groups could potentially reflect the following clinical scenarios- sunitinib patients who do not receive a second line therapy are likely to be those patients that have a good duration of response to sunitinib; whereas patients who receive IFN first line and do not move onto a second line therapy are likely to be those patients who have progressed quickly on IFN and are no longer fit to receive a second line therapy.
- Unless there are clearly defined characteristics that allow pre-selection of this subgroup of the overall study population prior to initiation of therapy, a practical, generalisable cost-effectiveness analysis cannot be based upon this data.

Roche believes that it is most accurate and correct to compare the most recent PFS and OS hazard ratios for bevacizumab + IFN and sunitinib. The old data used by the assessment group led to the conclusion that sunitinib may be more effective than bevacizumab + IFN for both PFS and OS, and this result was stated by the assessment group to be statistically significant. Roche request that the assessment group re-analyse this data and are confident that such conclusions will not again be reached. Based on the indirect comparison methods stated by the assessment group in the appendix to their report Roche has re-calculated the sunitinib hazard ratios compared to bevacizumab + IFN, and suggest that the assessment group should also re-calculate their estimates in order to confirm the Roche figures and to confirm the confidence intervals around these estimates.

Table 2: Indirect Comparison of Bevacizumab + IFN and Sunitinib utilising most recent published evidence

	Hazard Ratios (compared to IFN)			**Indirect Comparison – Sunitinib Vs Bevacizumab + IFN**	
	Bevacizumab + IFN safety population (ITT population)	**Sunitinib old data**	**Sunitnib new data**	**Old data, calculated by Assessment Group (95% CI)**	**New data, safety population (ITT population)**
PFS	0.61 (0.63)	0.42	0.54	0.67 (0.50 – 0.89)	0.89 (0.86)
OS	0.71 (0.79)	0.65	0.82	0.82 (0.53 – 1.28)	1.16 (1.04)

Based on the results of this indirect comparison the PFS hazard ratio for sunitinib compared to bevacizumab + IFN increases and Roche suggests that the confidence intervals for this estimate will cross unity – Roche believe that the assessment group should reanalyse the data in order to calculate these confidence intervals. For OS the confidence intervals are also likely to cross unity, but based on the most recent sunitinib data bevacizumab + IFN appears better than sunitinib. Roche suggests that this data should be considered as the most appropriate clinical data with which to draw any clinical comparison

between sunitinib and bevacizumab + IFN. In addition, this updated data should be used for sunitinib in the economic model. Roche suggests that this will not support the assessment group's current conclusion that sunitnib dominates bevacizumab + IFN.

3. Adverse Events

The assessment group admits that their approach to the inclusion of adverse events in the economic model is simplistic and represents a limitation of their analysis. The assessment group suggest that this is relatively unimportant however due to the small effect that adverse events have on the total treatment costs associated with IFN, sunitinib and bevacizumab + IFN. Roche acknowledge this, but feel that more representation of adverse events should be included in the economic model due to their importance to patients, and because the differing profile of adverse events between a bevacizumab + IFN treatment regimen and a sunitinib regimen both in terms of cost and possible quality of life impacts should be highlighted to the appraisal committee.

For example, some differences in the adverse event profiles between bevacizumab + IFN and sunitinib shown in Table 17 of the assessment group's report include the potentially expensive Hand-foot syndrome (experienced at grade 3 or 4 level by 5% of sunitinib patients and 0% of bevacizumab + IFN patients); Thrombocytopenia (experienced at grade 3 or 4 level by 8% of sunitinib patients, 2% of bevacizumab + IFN patients, and less than 1% of IFN patients); and Neutropenia (12% sunitinib, 4% bevacizumab + IFN, 2-7% IFN). The assessment group states that the inclusion of particular adverse events was decided by "an element of judgement, informed by clinical opinion" (pg. 151) but it is unclear why adverse events such as those listed above were not included in the analysis. Roche suggests that the adverse events chosen by the assessment group place sunitinib in a relatively favourable light compared to bevacizumab + IFN and that the adverse event profile is not as similar between the drugs as suggested by the assessment group. This is of importance both from a cost point of view and a quality of life point of view, particularly as recent data has shown the impact on quality of life of hand-foot syndrome (Huggins et al 2008).

In addition, it is important to consider that the incidence of side effects for sunitinib are those reported for the interim analysis published by Motzer (2007a), in which median exposure to sunitinib was six months. This data has been updated and presented at ASCO 2007 (Motzer 2007b) and there was an increased incidence of sunitinib toxicities when the median exposure was extended to 11 months, which is more comparable to the 10 month median exposure reported for bevacizumab in the AVOREN study. The differences in the incidence rates for these different data cut-off points are illustrated in Table 25 of the Roche submission to NICE. This shows that the incidence of Hand-foot syndrome had risen from 5% to 8% in the new data analysis, incidence of thrombocytopenia increased from 8% to 9%, and incidence of neutropenia increased from 12% to 16%. Hence using the most up to date data for sunitinib it

appears even more important to include some adverse events which were excluded by the assessment group.

The most recent Motzer data (2007b) also shows that hypothyroidism is associated with sunitinib treatment (11% all grades, 2% grade 3 or 4). This is not observed with bevacizumab and is potentially expensive because resources are required to undertake investigation and monitoring of patients' conditions. Some UK centres have now implemented routine monitoring of thyroid function for all patients receiving sunitinib, and recent data has illustrated further the relationship between sunitinib and thyroid dysfunction (Wolter et al 2008).

4. Safety Population

Roche note that the assessment group state that the ITT rather than the safety population data should be used in the analysis, and that it is unclear why Roche used the safety population data. Roche wish to point out that on page 64 of Roche's original submission it is stated that "For such an immature data set it is reasonable to consider the use of the safety population data, to ensure that data is only taken into account where patients received at least one dose of the study drug". Roche believes that this allows more accurate data to be analysed, particularly for the overall survival statistics which are based on very immature data.

In addition, Roche believes it is most appropriate to consider the safety population, ie patients who have received at least one dose of the drug, for the following reasons:

- In the setting of a randomised, double-blind, placebo controlled setting, it is unlikely that the reasons for not receiving the intervention are related to the drug itself, and are therefore random in nature. Despite randomisation, imbalances may occur that may inappropriately impact assessment of comparative efficacy. e.g. in Avoren 6 (1.8%) patients in the IFN arm did not receive the study drug (including one death), whereas only 2 (0.6%) patients in the Avastin + IFN arm did not receive the study drug.
- When assessing the costs associated with bevacizumab therapy there are no costs incurred prior to administration, therefore by definition the effectiveness should be assessed in those patients that have received at least one dose of drug. Ie because costs are calculated based on the treatment actually given, the effect sizes should only include data from patients who actually received the study drug.

Roche would also like to clarify to the appraisal committee that the choice of which population is analysed makes very little difference in the economic modelling. As stated by the assessment group the QALYs estimated for IFN and bevacizumab + IFN by Roche and the assessment group based on extrapolation of Kaplan-Meier curves and hazard ratios are almost identical and result in the same incremental benefit associated with bevacizumab + IFN.

5. Administration and Monitoring Costs

Roche note that the assessment group have used a different method to estimate administration and monitoring costs. The assessment group have used a Department of Health reference cost (2006/7) to estimate the cost of a chemotherapy infusion and have added separate monitoring costs, including a monthly outpatient medical oncology appointment with a consultant and one CT scan every 3 months while in PFS. Roche used one reference cost (2005/6) for an outpatient chemotherapy appointment which we assumed would cover both administration and monitoring of the patient. The primary reason for these different techniques is because the 2006/7 reference costs used by the assessment group were not available until February 2008, after Roche had made our original submission. The new reference costs are classed differently, with a cost per chemotherapy administration a new addition.

However, given the existence of the new reference cost categories, Roche believe that the cost applied to the administration of bevacizumab by the assessment group may not be appropriate. The administration of bevacizumab is very quick compared to other chemotherapies 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 reasonable given the average administration time of bevacizumab of approximately 30 minutes (in some centres it is administered in 10 minutes, following the Memorial Sloane-Kettering Cancer Centre publication, Reidy 2007), compared to commonly administered agents such as irinotecan, leucovorin, and other combination therapies which take an average of two hours to infuse for colorectal patients (see relevant Summary of Product Characteristics). Applying this administration cost would significantly reduce the treatment cost of bevacizumab + IFN and ignoring this issue biases the results against bevacizumab + IFN.

Roche also wish to take this opportunity to highlight to the Appraisal Committee the uncertainty surrounding the chemotherapy administration reference costs reported in 2006/7 (illustrated in Table 3, below). The reference costs show that the cost of the first delivery of a simple parenteral chemotherapy in an outpatient setting is £170 (HRG Code SB12Z), whereas the cost of the first delivery of a more complex parenteral chemotherapy in an outpatient setting is £104 (HRG Code SB13Z). This does not seem logical from a resource use perspective. Similarly it does not seem logical to apply the most expensive chemotherapy delivery reference cost (HRG SB15Z) to bevacizumab considering the short infusion time associated with the treatment. Notably, in NICE's recent FAD regarding the appraisal of erlotinib for the treatment of non-small-cell lung cancer the Appraisal Committee concluded that reference cost SB12Z was the most appropriate for the costing of a 60 minute docetaxel infusion [NICE, 2008].

Therefore to assume £197 (uprated from £189) for a 30 minute bevacizumab infusion seems both unfair and inconsistent with previous NICE methodology.

Table 3: National Schedule of Reference Costs 2006-07 - NHS Trusts: Chemotherapy Outpatients

HRG Code	HRG Label	No. of Patient Treatment Attendances	National Average Unit Cost (£)	Interquartile Range of Unit Costs [2]	
				Lower Quartile (£)	Upper Quartile (£)
SB11Z	Deliver exclusively Oral Chemotherapy	53,575	179	63	246
SB12Z	Deliver simple Parenteral Chemotherapy at first attendance	28,056	170	67	284
SB13Z	Deliver more complex Parenteral Chemotherapy at first attendance	26,304	104	86	214
SB14Z	Deliver complex Chemotherapy, including prolonged infusional treatment at first attendance	45,588	179	90	297
SB15Z	Deliver subsequent elements of a chemotherapy cycle	134,026	189	95	242

Most importantly, the assessment group's assumptions regarding dose intensity seriously increase the administration costs estimated because the assessment group assume that treatment continues for much longer than actually occurred (12.0 months compared to 7.1 months). As such, many more administrations are costed than actually occurred, seriously biasing the results against bevacizumab + IFN. The assessment group estimate administration costs of £5,554 per patient for the administration of bevacizumab + IFN while Roche estimate £3,545 for this figure. By far the largest reason for the difference in these estimates is the number of administrations costed. Roche estimate that the assessment group's base case ICER would reduce to approximately £112,829 if the correct treatment duration was modelled for both drug use and administration, if a more reasonable administration cost is used for bevacizumab and if IFN administration costs are removed from the model. The ICER including the dose cap would fall to around £79,372. However Roche can not state these figures with certainty because the copy of the assessment group's model supplied to Roche cannot be directly adapted and therefore Roche request that the assessment group undertakes this analysis as a matter of urgency.

6. Progressive Disease Costs

The assessment group report that when in the progressive disease (PD) health state it is assumed that patients will be managed in primary care, and that they will have mean NHS resource use comprising one GP visit per month, 1.5 community nurse visits per month, and pain medications throughout the month. Roche feels that this is unrealistic because patients will certainly receive some kind of more intensive second-line treatment. The best data to use to inform this assumption is the post-protocol treatment data available from the relevant clinical

trials. Roche used this post protocol data in our submission. This helps progressive disease costs to be estimated more accurately, and also highlights any likely differences between treatment arms. In the Roche trial more second-line treatments were used in the IFN arm than in the bevacizumab + IFN arm, resulting in higher progressive disease costs for the IFN arm of the trial (described on pages 89-90 of the Roche submission). This is logical due to the more effective nature of the first-line treatment (bevacizumab + IFN). In the absence of other data, for an evidence-based analysis this represents the best data to use to inform the costs of the progressive disease health state, and not including this data biases cost effectiveness estimates against bevacizumab + IFN.

Roche estimates that including this data in the assessment group's economic model, as well as including the correct drug and administration duration, would reduce the assessment group's base case ICER to £108,567, and the ICER including the dose cap would fall to approximately £75,110. However Roche can not state these figures with certainty because the assessment group's model cannot be directly adapted by Roche, and therefore we request that the assessment group undertakes this analysis as a matter of urgency.

7. Overall Survival

The assessment group note that treatment crossover following interim analyses was permitted in all but one (temsirolimus vs. IFN) of the included trials resulting in confounding of overall survival data. The assessment group state that although overall survival data is promising, now that treatment crossover has occurred in the key trials further information from the randomised population will not be available. There is therefore a large amount of uncertainty surrounding the estimates of overall survival.

The assessment group go on to state that in all comparisons the estimates of cost effectiveness are most sensitive to variations in the hazard ratios for overall survival – when the OS hazard ratio falls, the ICER decreases. However, it is also stated that it is this data that is the most uncertain of any included in the model. In fact, the assessment group illustrate in table 46 that when the dose cap is included, and the lower bound for the bevacizumab + IFN OS hazard ratio is used in the model, the ICER falls to £49,190. Roche suggest that when the correct treatment administration duration is modeled this figure would fall even further. Additionally, given the immaturity of the OS data and the bias associated with post protocol treatments which will neutralise differential OS treatment effects associated with first-line treatment, Roche suggest that this represents a realistic estimate of the true cost effectiveness of bevacizumab + IFN compared to IFN monotherapy.

Roche firmly believes that the appraisal committee should consider these issues in their deliberations. Roche also believes that based on these facts it is unfair

for the assessment group to conclude that bevacizumab + IFN is unlikely to be considered cost effective at any reasonable willingness to pay threshold.

8. Counter-Intuitive PFS Effect

Roche wish to comment on the counter-intuitive PFS effect highlighted by the assessment group. The assessment group state that in the economic analysis improvements in progression free survival make the drugs less attractive in terms of value for money. Roche believe that this phenomenon is true across many different types of metastatic cancer and represents a challenge that must be faced by NICE and the Department of Health. Due to the cost effectiveness measures commonly used in the UK, the low value of benefits (QALYs) associated with effective new treatments in this disease setting means that it is very difficult to develop cost effective new drugs, particularly combination therapies which often add to already costly standards of care. This may disincentivise research in these areas and represents a significant threat with regards to future treatment advances for patients with these diseases.

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