BEVACIZUMAB, SORAFENIB, SUNITINIB AND TEMSIROLIMUS FOR RENAL CELL CARCINOMA.

DECISION SUPPORT UNIT

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1. INTRODUCTION

The DSU were asked to provide commentary on additional analyses submitted by the manufacturers Pfizer and Roche as part of this appraisal.
It is worth noting at the outset how the estimates of treatment effectiveness for overall survival (OS) and for progression free survival (PFS) influence estimates of cost effectiveness. There are three (inter related) issues which drive cost effectiveness:

1) The hazard ratios themselves
2) Baseline progression free and absolute survival estimates (i.e. the same HR applied to different baselines will result in higher absolute gains)
3) Impact of incremental gains in PFS and OS (i.e. because treatments are given until progression it is preferable in cost-effectiveness terms to minimise differences in PFS and maximise differences in OS).

These issues are important when considering the various sets of ICERs calculated below.

2. RESPONSE TO PFIZER ADDITIONAL ANALYSES OF CLINICAL EFFECTIVENESS

In their response to the ACD and in a previous letter dated 27th June 08, Pfizer submitted additional analyses on the clinical effectiveness of sunitinib. At the time of the original submission made by Pfizer, the trial A6181034 had only reported interim results. Median overall survival had not been reached.

When the final results from the trial are incorporated into the Pfizer cost-effectiveness model, the ICER rises from £29k per QALY to £72k per QALY. This is assumed to be based on a hazard ratio for OS rising from 0.65 in the interim analysis to 0.82 in the full ITT final analysis. Pfizer argue however that there is potential bias in the ITT estimates of overall survival and therefore an underestimate of the cost effectiveness of sunitinib. There are two potential sources of bias:

i) the IFN group that were allowed to cross over to sunitinib after the first interim analysis

ii) patients in both study arms that received second line systemic therapies

Pfizer present an analysis where patients in group (i) were censored at the time of cross over. The HR for OS is 0.81 in this situation. This makes little difference to the ICER compared to the full ITT analysis.

Pfizer argue that the appropriate estimate of both OS and PFS comes from their analysis that:

a) exclude all patients that received second line therapies. This results in a HR for OS of 0.65.
b) Adjust the PFS curve to obtain a better fit
c) Adjust the OS estimate

These three changes in combination result in an ICER of £31k per QALY.

In order to estimate the potential impact of these changes in the PenTAG model, a number of alternative ICERs are presented in Table 1 below. The base case scenario refers to the original hazard ratios applied by PenTAG for OS (0.65) and PFS (0.42). Alternative scenarios are based on the revised PFS data (investigator led or central reviewer analyses) and the revised full ITT OS data. The first 5 sets of results do not include the agreed pricing strategy of the first cycle of sunitinib free to the NHS. The last row of Table 1 reports the impact of the agreed pricing strategy based on the results of the central reviewer analysis. Table 2 reports more detailed results based on this scenario.

Table 1: DSU revised cost-effectiveness estimates for sunitinib using final HRs and PENTAG model

Scenario	**Inputs**	**ICER using PENTAG model**
Sunitinib – Base Case	*HR OS = 0.65* *HR PFS = 0.42*	*£71,462*
Sunitinib – Revised PFS data Investigator led HR PFS	HR OS = 0.65 HR PFS = 0.52	£61,487
Sunitinib – Revised PFS data Central Reviewer analysis HR PFS	HR OS = 0.65 HR PFS = 0.54	£59,819

Sunitinib – Revised PFS + OS data Investigator led HR PFS + Revised HR OS	HR OS = 0.82 HR PFS = 0.52	£120,474
Sunitinib – Revised PFS + OS data Central Reviewer analysis HR PFS + Revised HR OS	HR OS = 0.82 HR PFS = 0.54	£118,005
Sunitinib – Revised PFS + OS data Central Reviewer analysis HR PFS + Revised HR OS *+ 1st cycle sunitinib free*	HR OS = 0.82 HR PFS = 0.54	£104,715*

* see detailed breakdown below

Table 2: Detailed cost-effectiveness analysis estimates from DSU analysis using PENTAG model

	Sunitinib	**IFN-α**	**Sunitinib vs IFN-α**
Life years	1.85	1.63	0.22
Progression free years	1.12	0.62	0.50
QALYS	1.39	1.19	0.20
Drug costs	£24,299	£2,952	£21,347
Drug admin	£0	£491	-£491
Monitoring costs	£1,494	£825	£669
Diagnostic costs	£669	£370	£299
AEs	£78	£4	£74
BSC in progressed disease	£2,766	£3,798	-£1,032
Total costs	£29,306	£8,438	£20,868
ICER			
Cost per QALY			**£104,715**

In relation to the analysis that excludes all patients that received a second line therapy, several cautions are appropriate.

Firstly, the use of second line therapies in the UK NHS must be considered in order to identify the appropriate subgroups of patients. Table 3 reports the systemic treatments received by patients post study discontinuation.

Table 3: Patients who received systemic therapy post study discontinuation (A6181034)

	Sunitinib, n (%) (n=323)	IFN-α, n (%) (n=359)
Any post-study treatment	182 (56)	213 (59)

Sunitinib	36 (11)	117 (33)
Other VEGF* Inhibitors	106 (33)	115 (32)
Cytokines	63 (20)	47 (13)
mTOR** Inhibitors	28 (9)	16 (4)
Chemotherapy	21 (6)	20 (6)

Secondly, excluding patients who progress and therefore require 2nd line therapy (regardless of whether their demographics are similar or not to those who remain included) will almost certainly produce inappropriate results since their reason for exclusion is inextricably linked to outcome, i.e. death. A more appropriate strategy would be to censor at the time at which they began 2nd line therapy, though this should be undertaken with caution too.

Modelling of clinical efficacy data adopts the approach used by PenTAG (estimated Weibull model using monthly data). Although Figure 4 shows that by modelling PFS for sunitinib and IFN groups separately a reasonably 'good fit' is achieved (though not when the HR estimate is used to adjust the IFN curve), Figure 5 for OS in the IFN group displays considerable 'lack of fit', and the input of 3.88 life-years in Table 5 for sunitinib is derived from the survival curve in Figure 5 using the HR, which must cast serious doubt on the validity of the associated ICER.

An additional scenario was considered by the DSU using the Committee's preferred assumptions for the scenario of no systemic treatment post study discontinuation analysis based on the Pfizer model. This scenario was based on the PFS data from the ITT final analysis for both the IFN-α and sunitinib arms (1.06 [12.72 months] and 1.74 [20.88 months] progression-free years respectively). For overall survival, data from the IFN-α 'no post study treatment' arm of 2.29 (27.48 months) life years was inputted and 3.13 (37.56 months) life years taken from the ITT final analysis was used for the sunitinib arm. The results are presented in Table 4. This approach resulted in an ICER of £49,304 per QALY gained for sunitinib compared with IFN-α.

Table 4: Cost effectiveness analysis of no systemic treatment post study discontinuation analysis – DSU analysis based on Committee's preferred assumptions using Pfizer model

	Sunitinib	**IFN-α**	**Sunitinib vs IFN-α**
Life years	3.13	2.29	0.84
Progression free years	1.74	1.06	0.68

QALYs	2.33	1.69	0.64
Drug costs	£37,582	£6,096	£31,485
Follow-up costs	£2,476	£3,953	-£1,477
Diagnostic tests	£1,191	£736	£455
AEs	£73	£4	£69
BSC in progressed disease	£12,898	£11,758	-£1,140
Total costs	£54,220	£22,547	£31,673
*First cycle of sunitinib free			
ICERs			
Cost/QALY			**£49,304**

It is worth noting that this ICER is still likely to be an underestimate since the mean overall survival estimate applied to sunitinib in this scenario was based on the results from the overall ITT population. This estimate will include any additional survival benefits conferred to the proportion of subjects who subsequently received post-study treatments. Consequently, employing this estimate directly within this scenario represents the most optimistic assumption in relation to the estimate of mean overall survival for sunitnib in the absence of subsequent treatments i.e. that post-study treatments conferred no additional survival benefits within the ITT population.

3. RESPONSE TO ROCHE ACD COMMENTARY

3.1. OVERALL SURVIVAL / POST PROGRESSION TREATMENT EFFECT.

The hazard ratio used by both the AG and Roche is derived from the AVOREN trial.

In the AG cost effectiveness model, the HR for overall survival was taken from the intention to treat population, stratified according by MSKCC risk group and region (hazard ratio of 0.75 (95% CI 0.58 to 0.97); p=0.02670). The unstratified analysis that was not used in the model gave similar results (hazard ratio of 0.79 (95% CI 0.62 to 1.02); p=0.0670). (see page 51 of the assessment report).

In their original submission Roche based their analysis on the safety population (i.e. patients that had at least one dose of the treatment), stratified according to the trial protocol, which gave a slightly lower hazard ratio (HR of 0.709 (CI 0.55 to 0.91). Their justification for using this population, as opposed to the ITT population, is that this ensures that patients have received at least one dose of the treatment. There were

2 patients in the bevacizumab arm and 6 in the IFN arm that withdrew before the first treatment according to the published study paper (Escudier et al, 2007. p 2106). The HR for this population is 0.71. It is not clear if this is the definition used by Roche since in their letter they refer to 641 patients in the ITT population (Table 1), which would appear to be the safety population using the figures in the Escudier et al. paper. In their original submission they refer to 649 in the ITT population

The ITT analysis should be considered preferable to the safety analysis since this is the basis on which patients were randomised. The safety analysis permits patients originally randomised to the IFN arm to be analysed as part of the bevacizumab arm if they received one or more doses. Efficacy analyses should be conducted on the ITT population as in the PenTAG model with appropriate consideration of costs for patients that did not actually receive treatment, thus allowing appropriate modelling of patients that do and do not comply with treatment.

Table 5 reports the revised ICERs, based on the PENTAG model, incorporating the safety population estimates for (i) the HR for OS and (ii) the HR for OS and PFS.

Table 5: Revised cost-effectiveness for bevacizumab using safety population

Scenario	**Inputs**	**ICER using PENTAG model**
Bevacizumab – Base Case	*HR OS = 0.75* *HR PFS = 0.63*	*£171,301*
i) Bevacizumab – Revised OS data Safety population	HR OS = 0.709 HR PFS = 0.63	£144,303
ii) Bevacizumab – Revised OS and PFS data Safety population	HR OS = 0.709 HR PFS = 0.609	£147,718

In their response to the ACD, Roche raise an additional issue. Overall survival may be confounded in trials where patients switch to other treatments after disease progression or treatment failure. In this situation, the comparator group may gain survival benefits from these second line treatments. Therefore, the cost effectiveness modelling should either include the costs of providing these additional treatments to patients in the comparator arm (as Roche argued their model did) or factor out the

survival benefits attributable to the second line treatments. Since the assessment group did not have access to the patient level data, they were unable to perform such an adjustment. Roche present results based on censoring all patients that received second line treatments and stratifying as in the previous analyses (hazard ratio of 0.613 (CI 0.46 to 0.81). This results in a substantial reduction in the numbers of patients included in the analysis from 641 in the ITT population, although see previous paragraph for concerns about whether this is in fact the safety population (325 bevacixumab + IFN vs 316 IFN) to 147 (91 bevacixumab + IFN vs 56 IFN).

The impact of implementing this revised estimate in the PenTAG model is reported below in Table 6.

Table 6: Revised cost-effectiveness for bevacizumab using adjusted HR for OS

Scenario	**Inputs**	**ICER using PENTAG model**
Bevacizumab – Base Case	*HR OS = 0.75* *HR PFS = 0.63*	*£171,301*
Bevacizumab – Revised OS data Adjusted analysis	HR OS = 0.613 HR PFS = 0.63	£101,340
Bevacizumab – Revised OS HR equivalent to HR for PFS	HR OS = 0.63 HR PFS = 0.63	£107,489

There is a difficulty that arises from these differences in approach. The ITT overall survival analysis respects the original trial randomisation whilst the censored analysis is based on particularly small numbers of patients. The patient groups are not entirely balanced in terms of their baseline characteristics between the censored treatment and control groups or between the censored groups and the ITT population, although it is difficult to assess whether these differences should be considered significant. Furthermore, there is a risk of unobserved differences between the treatment and control censored groups influencing the estimated treatment effect. It should also be noted that the revised estimate is more favourable than the HR for PFS which seems optimistic. For this reason we have also included a scenario that considers a HR of 0.63 for OS, equivalent to PFS.

The DSU suggest that provision of the individual patient data (IPD) would permit detailed consideration of the performance and credibility of alternative modelling strategies. In the absence of provision of this data a number of alternative analyses could be presented that demonstrate the impact of different approaches to censoring.

The alternative modelling approach would be to amend the PenTAG model to include the costs of second line therapies whilst maintaining the survival benefit estimates from the ITT population. This may then result in modelling of treatment strategies that do not reflect current UK NHS practice.

3.2. AVERAGE CUMULATIVE DOSE ADMINISTERED PER PATIENT

The AG calculate the cost of bevacizumab from three elements: the BNF unit cost, mean dose intensity reported from Escudier et al. (2007) and the mean duration of treatment.

Roche suggest that the actual mean dose observed in the trial safety population should be used to estimate the drug costs, as in the Roche model. However, it is not clear the source of the Roche calculations. In their original submission (p. 67), the dosages based on the safety populations are presented. However, these are based on populations larger (n= 336) than those reported randomised to this arm of the trial (n=327). PenTAG highlighted inconsistencies between these data and the dose intensities reported elsewhere in the original Roche submission and the trial publication (see page 119 of the AG report).

Nevertheless, the key area of disagreement between the PenTAG and Roche approaches relates to the definition of dose intensity. Mean dose intensity should report the amount of drug administered in a clinical trial as a proportion of the amount that would have been administered had there been no withdrawals or dose reductions. According to the protocol in the AVOREN trial, no dose reductions were permitted (Escudier et al. 2007, p 2105). Therefore, were the trial protocol adhered to, the figure of 88% used in the PenTAG model should reflect patients with disease progression, toxicity, or withdrawal of consent. Provided the PenTAG model appropriately reflects

withdrawals from treatment for these reasons, the application of this figure until progression would be appropriate and reflects the study protocol.

Roche argue that the dose intensity figures are only applicable to the actual treatment period of the trial i.e. the dose intensity figures do not reflect withdrawals at all but only the dose administered to those still receiving treatment.
Since the mean treatment duration is significantly shorter than the time to progression, due in large part to withdrawals due to adverse events, there is a difference in the drug costs calculated by the Roche and PenTAG methods.
This requires clarification from Roche.

One additional issue relates to how this is reflected in the model. Clearly, if patients remain in the progression free state beyond the 24 months of the trial then it is reasonable to extrapolate drug costs beyond that time in order to be consistent with the modelling of health benefits. Solely using the drug use reported within the trial would therefore be an underestimate. Due to censoring, not all patients have progressed at final follow up.

If the definition of dose intensity is as implied by the Roche comments, then the true drug cost is likely to lie somewhere between the PenTAG and Roche estimates.

3.3. NUMBER OF ADMINISTRATIONS.

The issue raised by Roche is similar to b) discussed above. PenTAG model the per protocol drug use and are consistent between the costing approach and the modelling of benefits.

Roche highlight two reasons why this approach does not correspond to the actual drug use in the trial. Firstly, as in the previous point, treatment duration was shorter than time to progression. This is likely to be mainly because of patients who withdrew from treatment due to toxicity. In addition, the protocol defined infusions every two weeks was not in fact followed. Infusions were given on average every 16.5 days, not every 14 days.

With regard to the second point, if the dose intensity figures cited above were correct, then the decreased frequency of infusions would form part of the dose intensity figure. It is therefore important that any corrections do not double count this element of drug costs.

The relevance of the difference between treatment duration and time to progression is as discussed above. However, in relation to this issue it is important to reiterate that censoring of patients within the trial means that a failure to model costs beyond that observed within the trial period would lead to an underestimate.

3.4. UNIT COST OF ADMINISTRATIONS

Roche argue that it is inconsistent to apply a unit cost using reference costs that relate to an average chemotherapy administration when bevacizumab requires a relatively short infusion of approximately half an hour.

The SPC for bevacizumab indicates that the first two infusions should be given over a longer period and subsequent infusions would then take approximately half an hour provided there has been no intolerance. The frequency with which intolerance is experienced should be considered in adjusting these administration costs.

The PenTAG model applies the same cost to administration of temsirolimus which requires a 30 to 60 minute infusion. Patients should be given intravenous diphenhydramine 25 to 50 mg (or similar antihistamine) approximately 30 minutes before the start of each dose. It does therefore seem appropriate to apply a lower cost to bevacizumab infusions.

Reference costs based on HRGs are not ideal for differentiating between treatments in this situation. Roche suggest the application of the lower quartile which is £95 compared to £189 (at 2006/7 prices), a near halving of the cost. This is an arbitrary figure.

It should also be noted that in the appraisal of erlotinib, Roche argued that a unit cost of £299 is applicable for docetaxel infusions, which last approximately one hour. In

this appraisal, the ACD states "the Committee noted that the most appropriate NHS reference cost (SB12Z) puts it in this range (at £170 per case)."

The degree to which this cost should be reduced requires consideration of the resources used in providing infusions. There are likely to be elements of this activity that do not vary with the duration of the infusion e.g. the set up, putting away equipment, preparation of patients, and this should inform the extent to which the unit cost is reduced from that used for an average infusion.

Table 7: Revised cost-effectiveness for bevacizumab using alternative costing assumptions

Costing Assumption	**Base-Case** *HR OS = 0.75* *HR PFS = 0.63*	**Scenario 1** *HR OS = 0.613* *HR PFS = 0.63*	**Scenario 2** *HR OS = 0.63* *HR PFS = 0.63*
Bevacizumab – Base case costings	£171,301	£101,340	£107,489
(i) Bevacizumab – Revised dosage only	£124,402	£74,008	£78,406
(ii) Bevacizumab – Revised dosage AND Revised number of adminstrations	£114,624	£68,561	£72,610
(iii) Bevacizumab – Revised dosage AND revised number of administrations AND revised unit cost of administration	£108,835	£65,213	£73,146

Table 7 shows revised cost effectiveness estimates based on the PenTAG model using the parameter values suggested by Roche in relation to costings. Because of the issues highlighted above in relation to the post hoc analyses, we present results for different overall survival HRs.

The table shows the impact of reducing (i) the dosage only, (ii) reducing dosage and number of administrations, (iii) reducing dosage and number of administrations and the unit cost of administrations.