NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment

Response to consultee, commentator and public comments on the Appraisal Consultation Document (ACD)

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the manufacturer or sponsor of the technology, national professional organisations, national patient organisations, the Department of Health and the Welsh Assembly Government and relevant NHS organisations in England. Consultee organisations are invited to submit evidence and/or statements and respond to consultations. They are also have right to appeal against the Final Appraisal Determination (FAD). Consultee organisations representing patients/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee.

Clinical specialists and patient experts – Nominated specialists/experts have the opportunity to make comments on the ACD separately from the organisations that nominated them. They do not have the right of appeal against the FAD other than through the nominating organisation.

Commentators – Organisations that engage in the appraisal process but that are not asked to prepare an evidence submission or statement. They are invited to respond to consultations but, unlike consultees, they do not have the right of appeal against the FAD. These organisations include manufacturers of comparator technologies, NHS Quality Improvement Scotland, the relevant National Collaborating Centre (a group commissioned by the Institute to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups (for example, the NHS Confederation, NHS Information Authority and NHS Purchasing and Supplies Agency, and the *British National Formulary*).

Public – Members of the public have the opportunity to comment on the ACD when it is posted on the Institute's web site 5 days after it is sent to consultees and commentators. These comments are usually presented to the appraisal committee in full, but may be summarised by the Institute secretariat – for example when many letters, emails and web site comments are received and recurring themes can be identified.

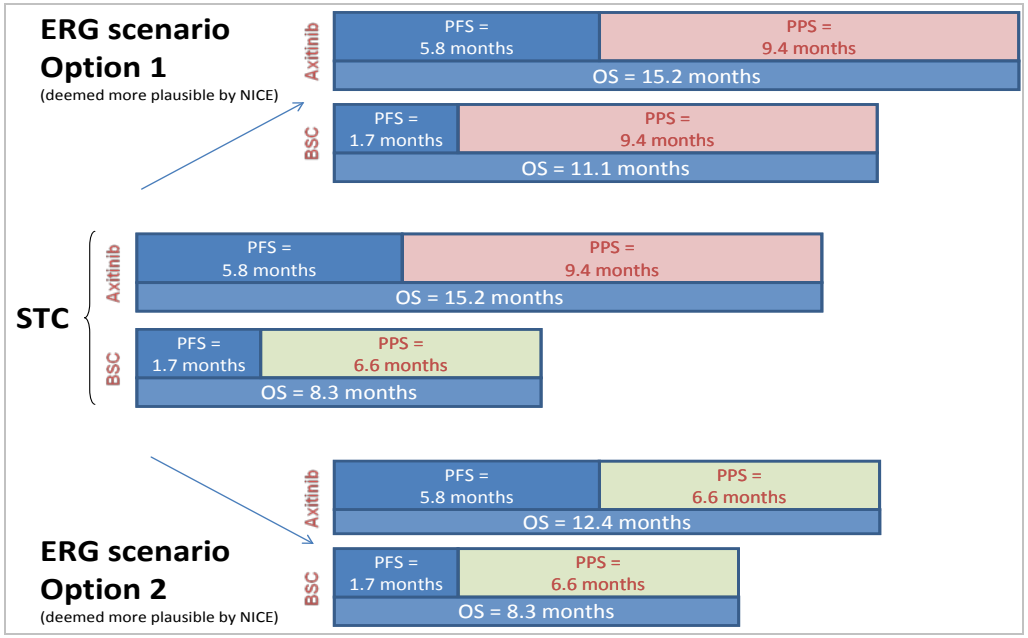
Comments received from consultees

Consultee	Comment	Response
Pfizer Limited	**1. Has all of the relevant evidence been taken into account?** **1.1 Simulated Treatment Comparison Adjustment Factors, Confidence Intervals and Standard Errors** In Section 4.7 in ACD "The Committee was aware that no confidence intervals or standard errors were provided to assess the uncertainties" of STC. In section 3.20 "The ERG also stated that the results of the comparison could not be verified because individual patient data from the AXIS trial were used; and the uncertainties around the results could not be assessed because standard errors and 95% confidence intervals were not presented". In order to address the ERG's and Committee's concerns about the validity and reliability of the STC due to the lack of CIs or SE around the adjustment factors, we have developed the methodology to estimate these CIs and SE, which is described in Appendix 1. This methodology should be considered along with the STC methodology described in Section 6.7.11 and Appendix 16 of the original evidence submission. The adjustment factors for which the CI and SE are estimated below in Appendix 1 are presented in Section 6.7.11 (page 103 and 106) and Section 7.3.6 (Table 40) of the original evidence submission.	Comment noted. Section 3.25 of the FAD has been updated to recognise the provision of the standard errors and confidence intervals. Section 4.8 of the FAD has also been updated to include the Committee's discussion on the confidence intervals provided.
	2. Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? For the prior sunitinib population, we believe that the ERG exploratory scenario considered more plausible by NICE, which resulted in a cost per QALY of £62,108 (with the PAS in the evidence submission), applies clinical assumptions that are unreasonable interpretations of the evidence. In responding to this question, we highlight the key elements of the STC and assess the validity of the results in the context of available clinical evidence. We then provide the clinical rationale to demonstrate why the assumptions underpinning the ERG exploratory scenario should be considered clinically implausible. Please note that in this scenario, the ERG assumed no difference in QALY gains for axitinib over BSC in the PPS period. This means that the PPS was assumed to be the same for both axitinib and BSC (i.e. no clinical or survival benefit of axitinib over BSC after the RECIST-defined progression period) based on the assumption used in our model that the utility values for the PPS period were the same for both axitinib and BSC. *QALY axitinib PPS = (axitinib PPS x utility PPS) = QALY BSC PPS= (BSC PPS x utility PPS), which results in axitinib PPS = BSC PPS*	The Committee considered this comment together with those from other consultees regarding the post-progression survival benefits. Its discussion and conclusion have been updated in section 4.15 of the FAD.

Consultee	Comment	Response
	2.1 The Simulated Treatment Comparison Given the importance of the STC results to this appraisal, we have summarised the key elements of the rationale for using this method followed by a brief description of the methodology and the results of the STC below. *(See sections 2.1.1 – 2.1.3 of the manufacturer's comments on the ACD for full details of the STC)*	Comment noted. Section 3.43 of the FAD has been updated to include the ERG's comment that the additional details of the STC provided were clearer than those in the original submission. Section 4.7 and 4.8 of the FAD describe the Committee's views on the STC methodology.
	2.2 Evidence Review Group Additional Exploratory Analysis is Clinically Implausible and Inconsistent with Conclusions in Previous mRCC Appraisals and Committee's Conclusions for the Cytokine Refractory Results The ERG additional exploratory analysis was driven by how QALYs accumulate in our base case analysis for axitinib versus BSC before and after progression for the two subgroups (i.e. cytokine-refractory and sunitinib-refractory patients). They noted that in our base case analysis for the cytokine-refractory patients the number of QALYs accumulated after progression are the same for the axitinib and BSC arm, and therefore there was no QALY gain for axitinib over BSC. Given that the utilities used in the model were assumed to be the same for both axitinib and BSC before and after progression, no QALY gain post progression means no survival gain post progression. As noted above, this is in contrast to what has been reported in other second-line mRCC clinical trials, which have compared targeted therapies with BSC, and what is estimated by the STC analysis for the prior sunitinib patients. Based on the clinical data and rationale described above, it is anticipated that a targeted therapy such as axitinib, when compared to BSC, will result in survival gains both before and after progression. Importantly, in section 4.12 of the ACD *the Committee discussed the plausibility of the survival gains estimated for the prior-cytokine group from the economic model. The Committee heard from the clinical specialists and patient experts that the overall survival of approximately 24 months in the best supportive care group of the prior-cytokine group is not seen clinically. It noted the manufacturer's comment that the implausibility observed may have resulted from the overall survival of 14 months in the placebo arm of TARGET which was not properly adjusted for crossover. The Committee considered that this possible over-estimation of the overall survival of BSC in TARGET was carried over into the overall survival results in the indirect comparison and ultimately affected the model results for the best supportive care group.* Therefore, the overestimation of the PPS in the BSC arm in TARGET, which was due to 48% of patients crossing over to sorafenib, resulted in an underestimation of the PPS gain of axitinib versus BSC.	Section 4.15 of the FAD now describes the Committee's consideration of this issue and states that *"The Committee considered the manufacturer's comments from consultation that some evidence exists from metastatic renal cell carcinoma trials that show that there are QALY gains in the post-progression period above those gained in the progression-free period when targeted therapies are compared with best supportive care. It heard from the manufacturer that active targeted treatments are associated with higher response rates and tumour shrinkage compared with best supportive care. The Committee examined the plausibility of a post-progression survival gain with axitinib in the context of the progression-free and overall survival relationship presented by the manufacturer (see section 3.26 of the FAD). It compared the relationship estimated from the manufacturer's simulated treatment comparison (1 to 1.6) and that originally modelled by the ERG (1 to 1). It noted that the relationship reported in the earlier version of the meta-analysis referenced by the manufacturer had been weakened by the inclusion of more studies where cross-over occurred in the updated meta-analysis (1 to 1.04 for the subgroup of trials with prior treatment and 1 to 1.29 for the subgroup where cross-over was adjusted). The Committee discussed whether it was plausible that a relationship of 1 to 1.6 would be observed when a*

Consultee	Comment	Response
		tyrosine kinase inhibitor is used after failure of a previous tyrosine kinase inhibitor. The Committee also noted the lack of post-progression benefit in the Axis trial for the prior-sunitinib group, as well as for the prior-cytokine group derived from the manufacturer's model.
	In addition, a median OS of 24 months would have been clinically implausible even in first line mRCC patients receiving cytokines where response to treatment is only seen in a small select population. Of note, the NICE appraisal of sunitinib for the first-line treatment of mRCC patients was based on an OS analysis which estimated that the median OS for cytokine patients who have not received post-study treatments was around 14 months. Despite this clear rationale, the ERG questioned whether there is a good reason why prior sunitinib patients receiving axitinib would have a QALY gain compared with BSC after progression, while prior cytokine patients do not. Thus they performed a scenario analysis in which it was assumed that for the prior sunitinib patients there was no difference in survival benefit after progression. This approach resulted in an ICER of approximately £62,108 per QALY gained (with the PAS applied in the evidence submission). Subsequently the NICE appraisal committee considered that this scenario explored by the ERG represents a more plausible (although still uncertain) ICER for the prior-sunitinib group, and concluded that axitinib could not be considered to be a cost-effective use of NHS resources, as the ICER of £62,108 (with the PAS applied in the evidence submission) would have been higher than previously acceptable ICERs for end-of-life treatments. The ERG exploratory analysis and the NICE appraisal committee draft recommendation is therefore inconsistent to what the Committee concluded regarding the results of our base case for the prior cytokine population, acknowledging the unlikely high OS for BSC. Therefore, the Committee and the ERG used the lack of PPS gains for axitinib versus BSC in the prior cytokine population, which were considered to be underestimated and clinically implausible by clinical experts, patient groups and the Committee itself to adjust the prior sunitinib results. It is important to note that clinical experts and patients groups during the Committee found the STC results to be clinically plausible. In addition, in section 2.1.3 above, the STC findings were found to be consistent with clinical evidence from second-line mRCC trials comparing targeted therapies with BSC.	Comment noted. The Committee concluded that the progression-frees survival and overall survival relationship for the prior-sunitinib group was likely to lie between the manufacturer's estimate and the ERG's estimate, although probably closer to the ERG's estimate (see FAD section 4.15).

Consultee	Comment	Response
	Furthermore, the ERG did not provide sufficient information regarding the assumed PPS for axitinib and BSC in this scenario. This, therefore, did not allow for assessment of the clinical plausibility of the necessary assumptions and adjustments to the estimates of OS for axitinib and BSC (which would have resulted in no QALYs post progression). In addition to the inconsistencies of the ERG exploratory analysis identified above, in order to further assess the internal and external validity of the ERG exploratory analysis we have identified two likely scenarios for the adjusted PFS and OS estimates for axitinib and BSC, assuming no QALY/survival gain post progression. These scenarios were identified based on PPS estimates in the STC, which reflect the Phase III RCTs for axitinib and BSC in the prior sunitinib population. Given that only the AXIS and RECORD-1 trials reported survival estimates for axitinib and BSC, respectively, the PPS in the ERG exploratory analysis would have been either approximately 9.4 months (15.2 months OS – 5.8 months PFS for axitinib in STC) or 6.6 months (8.3 months OS – 1.7 months PFS for BSC in STC) for both axitinib and BSC. Assuming 9.4 months PPS, the OS in the ERG exploratory analysis would have been approximately 15.2 months (5.8 months PFS + 9.4 months PPS) for axitinib and approximately 11.1 months for BSC (1.7 months PFS + 9.4 months PPS). Assuming 6.6 months PPS, the OS in the ERG exploratory analysis would have been approximately 12.4 months (5.8 months PFS + 6.6 months PPS) for axitinib and approximately 8.3 months for BSC (1.7 months PFS + 6.6 months PPS) – see Figure 8. Real-world evidence suggests that the median OS of patients on BSC following progression on sunitinib in the UK ranges from 4 to 6 months, which was previously highlighted in the everolimus NICE submission. Therefore, the results in ERG scenario 1 (Figure 8) over-estimate the survival on BSC. The BSC OS estimate in scenario 1 is also higher than the median OS with RPSFT (10.0 months) in ITT RECORD-1 BSC patients who had better MSKCC score, and thus further questioning the validity of the assumptions used in this exploratory analysis. In addition, axitinib OS in ERG scenario 2 was 12.4 months, which is inconsistent with the median OS estimate of 15.2 months from the AXIS study for prior sunitinib patients.	Comment noted. The Committee concluded that the progression-frees survival and overall survival relationship for the prior-sunitinib group was likely to lie between the manufacturer's estimate and the ERG's estimate, although probably closer to the ERG's estimate (see FAD section 4.15).

Consultee	Comment	Response
	Figure 8: Evidence Review Group Scenarios 	Comment noted.
	2.3 Sensitivity Analyses Results for the Prior Cytokine Population Suggests Base Case Incremental Cost-effectiveness Ratio is Overestimated *Section 3.41: Given the result of the sensitivity analyses, the ERG concluded that the model for the prior cytokine group was not very robust, with respect to most of the structural assumptions.* *The ERG undertook exploratory analyses within which adjustments were made to some of the parameters used in the manufacturer's base-case sensitivity analysis. It varied the model input parameters using the 95% CI provided by the manufacturer in response to the ERG and NICE clarification questions. The most evident difference from the manufacturer's analysis was observed when the OS hazard ratio for the prior cytokine group was varied. The manufacturer's base-case result of £65,326 per QALY gained was very sensitive to this change, which resulted in an ICER range £42,647–423,083 per QALY gained (with the PAS applied in the evidence submission).*	Comment noted. Section 4.6 of the FAD describes the Committee's discussions and conclusion on the prior-cytokine group and robustness of the results of the indirect comparison performed for this group. Section 4.12 of the FAD now states that *"The Committee concluded that the ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) may have been over-estimated based on the unlikely overall*

Consultee	Comment	Response
	In section 4.12 of the ACD *the Committee discussed the plausibility of the survival gains estimated for the prior-cytokine group from the economic model. The Committee heard from the clinical specialists and patient experts that the overall survival of approximately 24 months (in the base case) for the best supportive care group of the prior-cytokine group is not seen clinically. It noted the manufacturer's comment that the implausibility observed may have resulted from the overall survival of 14 months in the placebo arm of TARGET which was not properly adjusted for crossover. The Committee considered that this possible over-estimation of the overall survival of best supportive care in TARGET was carried over into the overall survival results in the indirect comparison and ultimately affected the model results for the best supportive care group.* Therefore, the overestimation of the OS in the BSC arm in TARGET in the base case, which was due to 48% of patients crossing over to sorafenib, resulted in an underestimation of the OS gain of axitinib versus BSC in the base case.This provides a clear rationale as to why moving the conservative OS HR for axitinib used in the base case to higher values within the 95% CI will result in even more clinically implausible OS scenarios for BSC. For example, in the scenario when the upper limit of the 95% CI for the OS HR is used, which results in an ICER of £423,083 (in the base case in the evidence submission), the median OS for patient receiving BSC is more than 30 months (with a PFS of 3.7 months). The ICER and survival estimates for the PAS in the evidence submission, for lower and higher 95% CI values for the OS HR in the indirect comparison are shown in Table 5.	*survival gains with best supportive care in the prior-cytokine population, but that there were other uncertainties that might push the ICER higher."* Section 4.18 of the FAD now states that *"In the case of the prior-cytokine group the Committee considered that these were people who could receive sunitinib or pazopanib but no comparison had been available to establish the true benefit of axitinib in this group."*

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
Table 5: Incremental Cost-effectiveness Ratio and Survival Estimates for the Mean, Lower and Higher 95% CI Values for the Overall Survival Hazard Ratio in the Indirect Comparison
<table>
<tr><th>OS HR</th><th>Survival</th><th>Axitinib (median months)</th><th>BSC (median months)</th><th>Gain (median, months)</th><th>PFS gain: OS gain ratio</th><th>ICER (with PAS in the evidence submission)</th></tr>
<tr><td rowspan="2">0.63
(Base case)</td><td>PFS</td><td>11.5</td><td>3.7</td><td>7.8</td><td rowspan="2">1:1.1</td><td rowspan="2">£65,326</td></tr>
<tr><td>OS</td><td>33.3</td><td>24.0</td><td>7.3</td></tr>
<tr><td rowspan="2">0.99
(Upper 95% CI)</td><td>PFS</td><td>11.5</td><td>3.7</td><td>7.8</td><td rowspan="2">N/A</td><td rowspan="2">£423,083</td></tr>
<tr><td>OS</td><td>33.3</td><td>33.3</td><td>0</td></tr>
<tr><td rowspan="2">0.41
(Lower 95% CI)</td><td>PFS</td><td>11.5</td><td>3.7</td><td>7.8</td><td rowspan="2">1:1.8</td><td rowspan="2">£42,647</td></tr>
<tr><td>OS</td><td>33.3</td><td>17.6</td><td>15.7</td></tr>
</table>
Abbreviations: BSC, best supportive care; CI, confidence interval; ICER, incremental cost-effectiveness ratio; OS, overall survival; PAS, patient access scheme; PFS, progression-free survival.
When the lower 95% CI for OS HR was used, the OS for BSC in the prior cytokine population was 17.6 months which is close to the 14 months reported in TARGET. In this scenario, the PFS and OS results are in line with the findings above, which indicate that the PPS should be greater for axitinib over BSC. The ICER for this scenario was £42,647 with the PAS in the evidence submission, which is close to the base case ICER in the prior sunitinib population.
</td><td></td></tr>
<tr><td></td><td>
2.4 Rationale for Selection of Survival Distributions for Progression-Free Survival and Overall Survival
‘Section 3.38: The ERG accepted the manufacturer’s choice of the distributions used in the base-case and scenario analysis. However, it noted that in some cases, the method of selection of the distributions (based on the Akaike and Bayesian information criteria, visual inspection and anchoring) was unclear, with expert opinion always dominating the reason for selection, and, in one instance, the decision was based on expert opinion of clinical plausibility.’
</td><td>Comment noted.
Section 3.41of the FAD has been updated to state that the ERG accepted the manufacturer’s choice of the distributions used in the base-case and scenario analysis.</td></tr>
</table>

Consultee	Comment	Response
	To model axitinib efficacy data, PFS and OS were incorporated into the economic model using parametric survival curves to determine the proportion of patients in the PF, PD and death health states. The framework used follows the approach recommended in the NICE Decision Support Unit technical support document number 14. Patient level data on PFS and OS were based on the most recent June 2011 and November 1, 2011 data cut-off respectively. Patient-level data were analysed using, exponential, Weibull, Gompertz, lognormal and loglogistic distributions (using Stata 10.0). Data were fitted to the clinical survival data for the axitinib treatment arm separately for the cytokine refractory and sunitinib refractory subgroups (sorafenib data were not included as it is not a relevant comparator for the model). Of the five distributions tested, the three judged the best fits were included in the model, with the base case representing the most plausible survival estimate, and the two scenario analyses representing alternate options. To determine the best model fit, the following criteria were considered, with the most appropriate model identified based on a combination of these: • AIC/BIC – Model fits were evaluated using Akaike's information Criteria (AIC) and Bayesian Information Criteria (BIC) statistics. Lower AIC/BIC figures are indicative of a better statistical fit of the survival function of the Kaplan-Meier data • Visual Inspection – Visual inspection was carried out by plotting the projected survival curves overlaid with the Kaplan-Meier survival functions. Estimates were evaluated based on the goodness-of-fit of the parametric survival curve to the Kaplan-Meier curve during the trial period, and the clinical plausibility of the proportion of patients estimated to be surviving at the tails of the curve. Fits were first assessed by the economic modelling team and validated using clinical input from UK expert clinical opinion. • Anchoring – Wherever possible, extrapolation estimates were validated through comparison with more mature external data sources. The selected distributions for the base case in the cytokine- and sunitinib-refractory populations, along with the parametric model that had the best statistical fit, are shown in Table 6.	Comment noted. Section 3.41of the FAD has been updated to state that the ERG accepted the manufacturer's choice of the distributions used in the base-case and scenario analysis.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td></td><td>
Table 6: Selected Distributions for Axitinib
<table>
<tr><th></th><th>Survival</th><th>Cytokine refractory</th><th>Sunitinib refractory</th></tr>
<tr><td rowspan="2">Base case</td><td>PFS</td><td>Weibull</td><td>Weibull</td></tr>
<tr><td>OS</td><td>Weibull</td><td>Lognormal</td></tr>
<tr><td rowspan="2">Best fit (AIC/BIC)</td><td>PFS</td><td>Weibull</td><td>Lognormal</td></tr>
<tr><td>OS</td><td>Weibull</td><td>Lognormal</td></tr>
<tr><td>Best fit (AIC/BIC)
Proportional hazard model</td><td>PFS</td><td>Weibull</td><td>Weibull</td></tr>
<tr><td></td><td>OS</td><td>Weibull</td><td>Weibull</td></tr>
</table>
Overall, for three of the four curves that were fitted, the final choice for base case coincided with the curve showing the best statistical fit. Only for the PFS curve in the sunitinib-refractory group was the choice of the distribution used in the base case based on expert opinion rather than the best statistical fit, as this was considered clinically more plausible. The lognormal curve had the best fit, in terms of AIC and BIC for PFS in sunitinib-refractory population, but as it resulted in a survival estimate at the tail-end of the curve (considered clinically implausible), the Weibull model (was the second best-fit and produced an intermediate PFS estimate between lognormal and Gompertz), was chosen as base case.
</td><td>Comment noted.
Section 3.41of the FAD has been updated to state that the ERG accepted the manufacturer’s choice of the distributions used in the base-case and scenario analysis.</td></tr>
<tr><td></td><td>
2.5 Therapeutic Value of Using Axitinib After Failure of Prior Sunitinib
Section 4.5: The Committee also noted the comment from the Committee for Medicinal Products for Human Use members that there were uncertainties over the therapeutic value of using axitinib after failure of prior sunitinib and the rationale for preferring axitinib over everolimus in this group of people.
The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency adopted a positive opinion by absolute majority, recommending the granting of a marketing authorisation for axitinib after failure of prior treatment with sunitinib or a cytokine. In discussing the benefit-risk balance in the European Public Assessment Report, the CHMP stated that ‘Treatment with axitinib showed an improvement in the median progression free survival. Results in ORR supported the observed improvement in PFS. Axitinib showed a clear antitumour effect in patients with advanced RCC that have failed prior cytokine and sunitinib therapy. The results are considered to be mature, robust and of clinical relevance.
</td><td>Comment noted.</td></tr>
</table>

Consultee	Comment	Response
	Based on the safety data from the submitted studies, axitinib seems to be acceptably tolerated as monotherapy in patients with advanced RCC. There does not seem to be more AEs in subjects treated with axitinib compared to sorafenib, although the incidences of some of the individual AEs varies between the two treatment arms. The majority of adverse events were mild or modest in severity and relatively few patients discontinued therapy due to AEs.' We would like to clarify that the above comment in the ACD relates to a minority divergent opinion of four CHMP members to the majority recommendation, appended to the European Public Assessment Report. In the view of this minority, there were uncertainties over the therapeutic value of using axitinib after failure of prior sunitinib and the rationale for preferring axitinib over everolimus in this group of people. In relation to everolimus, it must be noted that everolimus was not licensed at the time of the trial design; AXIS was the first trial to compare against an active comparator, sorafenib, in second-line mRCC. There are no comparative Phase III RCT data for axitinib versus everolimus for patients with advanced second-line mRCC. Of note, as stated in the ACD, everolimus is not a comparator for this appraisal. The European Society of Medical Oncology (ESMO) has recently updated the 'Renal Cell Carcinoma: ESMO Clinical Practice Guidelines (CPG) for diagnosis, treatment and follow-up'. These guidelines are intended to provide the user with a set of recommendations for the best standards of cancer care, based on the findings of evidence-based medicine. Each CPG includes information on the incidence of the malignancy, diagnostic criteria, staging of disease and risk assessment, treatment plans and follow-up. In these guidelines axitinib is recommended as a standard second-line treatment option, with the highest level of evidence.	Comment noted.
	3. Are the provisional recommendations sound and a suitable basis for guidance to the NHS? We believe the Committee's draft recommendation is based upon a clinically implausible scenario, which assumes that patients on axitinib will have no QALY/survival gains post progression over BSC. We, therefore, have concerns about the draft recommendation in the ACD and we strongly believe that it is not a sound and suitable basis for guidance to the NHS. In fact, taking the above findings into consideration, there is strong evidence to support the clinical plausibility of the STC results, which indicate that the PPS is greater for axitinib over BSC. This is in-line with results reported in Phase III trials of active treatments versus BSC and consistent with what a NICE committee has previously considered plausible for second-line mRCC.	Comment noted. Section 4.7, 4.8, 4.13, 4.15, 4.16 and 4.19 explains the rationale behind the Committee's recommendation in the prior-sunitinib group.

Consultee	Comment	Response
Department of Health	The Department of Health confirmed that they had no substantive comment to make regarding this consultation.	Comment noted.
James Whale Fund for Kidney Cancer	**1. Clinical Effectiveness** The Committee have recommended that the drug axitinib (Inlyta®) should not be considered a good use of NHS resources for advanced renal cell carcinoma patients after failure of prior systemic treatment. This is despite axitinib's effectiveness at prolonging the life of kidney cancer patients compared to sorafenib in the AXIS trial and best supportive care in the simulated treatment comparison (STC). The decision by the Committee to not recommend axitinib for advanced renal cell carcinoma patients after failure of prior systemic treatment means that terminally ill kidney cancer patients are again denied access to effective, licensed second-line treatment on the NHS after failing on sunitinib (Sutent®) or cytokines. The Committee has acknowledged that axitinib meets the end-of-life criteria but yet still recommends that axitinib is not a good use of NHS resources. As noted in the ACD, the use of cytokines is diminishing with the recent advances in targeted therapies, and is currently only prescribed for about 10% of advanced kidney cancer patients. The majority of patients receive either sunitinib or pazopanib (Votrient®) as first line treatment; however, the axitinib marketing authorisation only allows for patients previously treated with cytokines or sunitinib, which does not reflect current clinical practice. The Committee has not taken into consideration the probability that axitinib could one day (in the near future) be used in combination with other cancer drugs to further extend the life expectancy of advanced renal cell carcinoma patients.	Comment noted. Section 4.3 of the FAD now states that *"The Committee heard from the clinical specialists that the use of cytokines is rapidly decreasing in clinical practice and only a few people currently receive them because most patients begin treatment with sunitinib or pazopanib."* Section 4.19 of the FAD describes the Committee's rationale regarding its decision that axitinib does not represent a cost-effective use of NHS resources despite being a life-extending, end-of-life treatment in the prior-sunitinib group. Comment noted. However, NICE can only appraise a technology within its current marketing authorisation.

Consultee	Comment	Response
	2. Health Economic Assessments We are disappointed that yet again another drug for the treatment of advanced renal cell carcinoma has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups: Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying patients access to life-prolonging treatments during a difficult time for both themselves and their families.	The Committee's recommendations are based on evidence of both clinical and cost effectiveness. Above a most plausible ICER of £20,000/QALY, judgements about the acceptability of the technology as an effective use of NHS resources are more likely to make reference to explicit factors including: the degree of uncertainty surrounding the ICERs, whether there are strong reasons to indicate that the assessment of the change in HRQL has been inadequately captured, and the innovative nature of the technology. Above an ICER of £30,000/QALY, the case for supporting the technology on these factors has to be increasingly strong (NICE Guide to the Methods of Technology Appraisal, sections 6.2.23 to 6.2.25). The Committee can attribute more value to the QALYs gained by people with end of life treatments, but this is not open-ended particularly where there is great uncertainty.
	3. Sub-optimal Treatments Available on the NHS It has been shown that advanced renal cell carcinoma patients given sequential drug treatment with targeted therapies have the best prognosis for survival. The Committee's recommendation could deny patients this treatment option, which offers hope and comfort to patients and their families trying to come to terms with a terminal illness. The UK's cancer death rate is currently 6% higher than the European average; NICE's decisions are having a profound effect on the way we treat our cancer patients and the quality of health care available to our citizens. It leaves UK renal cell carcinoma patients at a major disadvantage in terms of the availability of state-of-the-art cancer drugs, meaning that these patients are likely to die prematurely compared to the rest of Western Europe and the United States of America.	Comments noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submissions and the Evidence Review Group's critique of the manufacturer's submission.

Consultee	Comment	Response
	4. Patient Benefits The Committee do not seem to have consulted the patient experts to any great extent for the ACD and any evidence of patient benefits has been given little weight in the recommendation compared to the discussion of evidence on costs. We feel that the patient perspective must be included in the Final Appraisal Document (FAD) and given due weight if the Committee wish to present a balanced and rounded appraisal.	The views of clinical experts and patient/carer representatives were considered by the Appraisal Committee when formulating its recommendations. Sections 4. 2 and 4.20 of the FAD has been updated to reflect this.
	5. Equalities Statement Patients for whom sunitinib or pazopanib are not a therapeutic option because of intolerance or co-morbidities (e.g. congestive heart failure, poor nutritional state, impaired mobility, hypertension) and patients who are unsuitable for immunotherapy (due to e.g. organ impairment, presence of hepatic metastases, and contraindications such as liver dysfunction or brain metastases) are discriminated against and will not have any therapeutic option under the NHS. The equalities statement in the Appraisal Consultation Document is, therefore, untrue since not all patients are affected by the guidance in the same way. **Conclusions** Kidney cancer accounts for approximately 2% of all new cancers in the UK (approximately 9,000 people per year), and the incidence of kidney cancer is increasing. Advanced renal cell carcinoma affects about 4,000 people annually. Renal cell carcinoma is particularly difficult to treat and does not respond well to conventional cancer treatments, such as chemotherapy and radiotherapy. Once renal cell carcinoma spreads, targeted therapies, such as axitinib, are the only hope for these patients. The Committee's recommendation leaves clinicians with the choice of only two drugs (sunitinib and pazopanib) with which to treat terminally ill kidney cancer patients.	Any consideration of people who are not able to receive sunitinib, pazopanib or immunotherapy is beyond the scope of this appraisal as this would require axitinib to be appraised as a first line treatment in this group of people. NICE can only make recommendations within the current marketing authorisation of axitinib and in line with the agreed scope for the appraisal which is *"for the treatment of adults with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine."* The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submissions and the Evidence Review Group's critique of the manufacturer's submission before making its recommendations.

Consultee	Comment	Response
	If first line treatment is not effective or the patient is unable to tolerate it's side effects, patients are left with three choices; pay for a different drug themselves, appeal for funding through the Cancer Drugs Fund (which continues until March 2014) or Individual Funding Requests (which are invariably rejected by the local funding bodies who follow the lead of NICE), or palliative care while they wait to die. Appeals for funding can take anything up to 6 months to complete, during which time patients are receiving no active treatment, their cancer is progressing and their quality of life deteriorating. *In the light of the issues raised above the James Whale Fund for Kidney Cancer is of the view that the Committee's recommendation in relation to the patient who has no therapeutic option is a breach of Human Rights (Article 2-the right to life).*	Section 4.2 of the FAD has been updated to reflect that the Committee considered the comment on a potential breach of Article 2 of the Human Rights Act and it states that *"The Committee exercised due regard to NICE's commitment to promote equality, eliminate unlawful discrimination and actively consider the implications of its guidance for human rights, as stated in section 1.4 of the Guide to the methods of technology appraisal."*
Kidney Cancer UK	KCUK is most disappointed with the provisional conclusion of the ACD indicating that NICE is minded *not* to recommend axitinib for second-line treatment of RCC. In response to this, KCUK wishes to make the following points. **Availability of second-line treatments** If the ACD recommendation is enshrined in the Final Appraisal Determination (FAD) this would mean that NICE has failed to find in favour of *any* of the three drugs put forward for second-line treatment: sunitinib, everolimus and, now, axitinib. Such a situation compares unfavourably against the positions adopted in many other countries in which second-line treatment is routinely available in corresponding national health services.	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submissions and the Evidence Review Group's critique of the manufacturer's submission before making its recommendations.

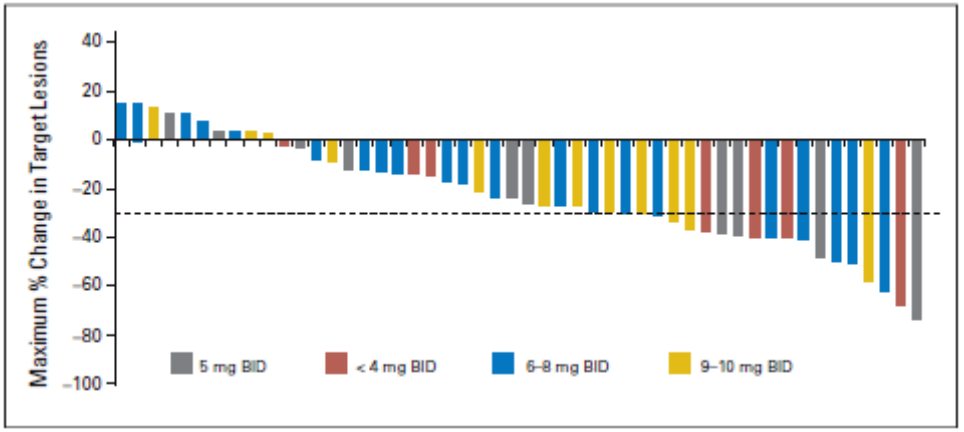
Consultee	Comment	Response
	Alternative drugs for second-line treatment In the course of this appraisal there has been some discussion over the relation between axitinib and everolimus, given that the latter is sometimes funded through the Cancer Drugs Fund (CDF). KCUK considers it important for drugs of this kind to be recognised as eligible for NHS funding, rather than just the CDF, which is both temporary and only available in England (and not in other countries of the UK). But KCUK has two further points on this. First, as attested to by the oncology consultees, it is valuable to have a number of drugs available for patients, since some patients often respond better to one drug than to the others. This is especially important where there are serious genomic factors involved. Specialist opinion is strongly behind having both a TKI (such as axitinib) and an mTOR inhibitor (such as everolimus) as second-line options. One suggestion is that patients who have benefited for less than 6 months from the first-line TKI (indicating that their diseases were not very sensitive to the modality of that treatment) should be considered for an mTOR inhibitor (eveolimus) for their second-line treatment, whilst those who have benefited more significantly from the first-line TKI (ie for more than 6 months) should be offered a further TKI (axitinib) for their second-line treatment. Thus, in this context, the two drugs can be viewed more as complements to each other rather than as substitutes. When either of these drugs is not recognised for funding, some patients could be said to be discriminated against, in only being offered sub-optimal second-line treatment.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers' submissions and the Evidence Review Group's critique of the manufacturer's submission before making its recommendations. The Committee's recommendations are based on evidence of both clinical and cost effectiveness of axitinib when compared with best supportive care as specified in the scope of the appraisal.
	A second point is that, however many different drugs there are, the total cost burden upon the NHS will remain broadly the same. On page 42 of the ACD (paragraph 4.17) it is noted that the estimated population for whom axitinib is licensed (1580 people in year 1 and up to 1743 people in year 5) represents a rather small number of patients overall Recognising axitinib together with everolimus would not make any significant difference to these numbers and consequently no material difference to the total costs borne by the NHS.	The Committee's decision is not determined by the potential budget impact of a new technology but rather the cost effectiveness in terms of how its advice may enable the more efficient use of available healthcare resources (NICE Guide to the Methods of Technology Appraisal, section 6.2.14).

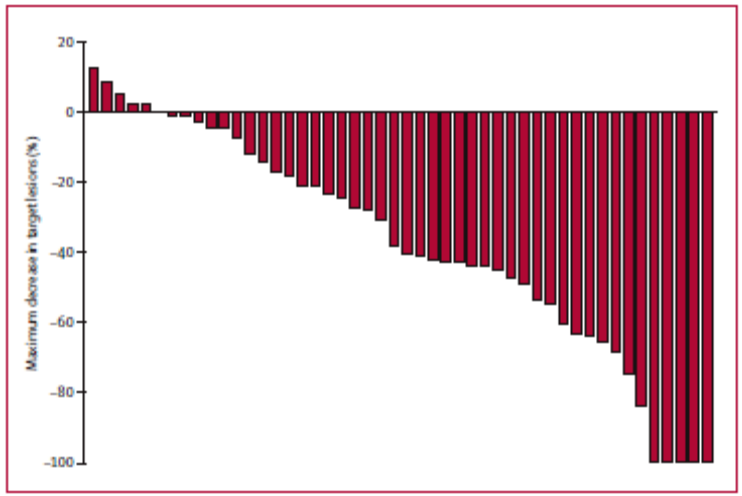
Consultee	Comment	Response
	Post-progression survival (P-PS) In paragraph 3.45 on ACD page 31, the length of P-PS is taken as being the same for axitinib plus best supportive care as it is for patient just receiving first-line treatment plus best supportive care. But is this a reasonable assumption to make? We understand that, in clinical practice, most patients survive on best supportive care for longer if they have had the second-line drug than if their active drug treatment finished with the first-line drug. In other words, there is a residual benefit here; and allowing for this would have the effect of reducing the calculated ICER, or cost per QALY, down from the figure of £62 000 in the direction of the lower estimate of £41 000.	The Committee considered this comment together with the manufacturer's comment on the post-progression survival gains. Section 4.13 and 4.15 of the FAD has been updated to capture its discussion and conclusion on the post-progression survival gains.

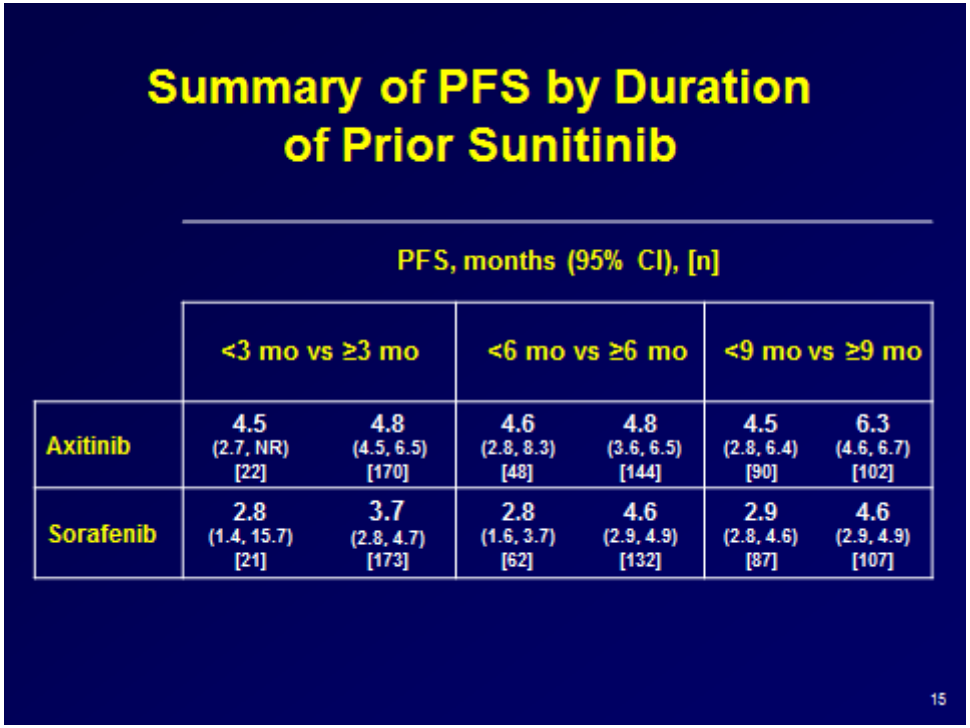
Comments received from clinical specialists and patient experts

Nominating organisation	Comment	Response
Clinical Specialist	**General points** 1. It does not seem helpful to go over differences of opinion in the CHMP now Axitinib is licenced. As indicated in my summary at the meeting Axitinib appears to be a more potent VEGF inhibitor and therefore it is entirely reasonable that there should be incomplete cross-resistance to other less potent VEGF inhibitors. In addition, there is indeed evidence that resistance to VEGF TKIs is reversible (Zhang et al., 2011).	Comment noted.

Nominating organisation	Comment	Response
	2. There is an obvious inherent flaw in the system that we are trying to estimate cost per QALY where all seem to agree there is insufficient data to define a cost per QALY accurately. What Axitinib has been shown to do is produce responses and PFS benefit in previously treated patients – responses in around 22.6% of patients (11.3% in prior sunitinib patients and around 32.5% in prior cytokine patients) and a PFS benefit of 2 months (5.6 months in prior cytokine patients and 1.4 months in prior sunitinib patients). These are entirely consistent with some but incomplete resistance following prior VEGF TKI exposure. These are also statistically significant and meaningful for patients – albeit somewhat limited in the sunitinib pre-treated group. There is no proven survival benefit in either group and that is increasingly common in kidney cancer studies where there are multiple potential salvage therapies available to confound the outcome. Hence in my view it would be far better to assess a cost per "quality adjusted PFS" rather than using complex adjustments of doubtful value to assess QALYs. These will always be very uncertain and is illustrated by the wide variation in all estimates regardless of who produces them and of the most plausible figure chosen!	The reference case specifies the methods considered by NICE to be the most appropriate for the Appraisal Committee's purpose and consistent with an NHS objective of maximising health gain from limited resources. (NICE Guide to the Methods of Technology Appraisal, section 5.2.2). The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per QALY. See Guide to the Methods of Technology Appraisal, section 5.1 (summary of the reference case).
	Specific Points In terms of the NICE accepted cost per QALY there appear to be a number of scenarios that have been examined most of which make little difference. The key question seems to be the post-Axitinib survival gain the modelling of the post treatment period. The point is made that this in not seen in the Axis trial result and also was not used in the model for post cytokine therapy. I will address each of this point separately;	Comment noted.

Nominating organisation	Comment	Response
	(i) Post-Axitinib it is certainly plausible that there will be a QALY gain as well as while on Axitinib. On stopping the treatment there will be some utility gain from reduction in side effects and also patients will on average start with less disease. There are no "waterfall plots" given in the Axis trial publication but previous publications suggest that even though the response rate may be low many patients have some reduction in the size of the tumour. Because of the way progression is calculated (30% increase from minimum size not from baseline) this will also mean the tumour burden is on average lower in those patients progressing after Axitinib (or any active therapy) than patients on placebo. Given the small difference in PFS and ORR between Sorafenib and Axitinib the difference may be small and not seen in the Axis results per se, but it would be larger compared to placebo which is the agreed relevant comparator. Thus I feel it is inappropriate to assume no benefit post progression as in section 4.13 of ACD. I cannot comment on whether the Pfizer assumptions are correct or if some compromise is more appropriate but either way it would reduce the ICER to nearer £50,000.  Figure 1 : Waterfall plot of tumour sizes from Rini et al., 2009 – a post Sorafenib population.	The Committee considered this comment together with the manufacturer's comment on the post-progression survival gains. Section 4.13 and 4.15 of the FAD has been updated to capture its discussion and conclusion on the post-progression survival gains. The conclusion states that *"The Committee concluded that the progression-frees survival and overall survival relationship for the prior-sunitinib group was likely to lie between the manufacturer's estimate and the ERG's estimate, although probably closer to the ERG's estimate."* Section 4.16 of the FAD also states that *"The Committee considered that the more plausible ICER for the prior-sunitinib group was likely to lie between the base case estimate with a survival relationship of 1 to 1.6 (approximately £33,500 per QALY gained) and the estimate assuming no survival gain with a survival relationship of 1 to 1(approximately £52,900 per QALY gained). Given the balance of the evidence, the Committee considered that the ICER would be closer to the higher estimate.*

Nominating organisation	Comment	Response
	(ii) Post –Cytokines, I feel the same comments apply but perhaps more so – the response rates are better and the extent of response tends to be better (see Figure 2). Again there are no published results from the Axis study but I have no reason to believe these are not similar. Again given the way progression is calculated I would expect a significant number of patients to have much lower disease bulk on progression and thus to survive longer (and perhaps to get other therapies). I cannot explain why the Pfizer model did not show this and we discussed this amply at the meeting. If this were properly taken into account, I believe, it would greatly reduce the ICER for the post-cytokine group – I accept this is a small patient population (probably less than 100 per year now).  Figure 2: Waterfall plot of tumour sizes from Rixi et al., 2007 – a post Cytokine population.	Comment noted. Section 4.12 of the FAD states that *"the Committee considered that this possible over-estimation of the overall survival in TARGET was carried over into the overall survival results in the indirect comparison and ultimately affected the model results for the best supportive care group. The Committee concluded that the ICER of approximately £55,300 per QALY gained (with the patient access scheme applied) may have been over-estimated based on the unlikely overall survival gains with best supportive care in the prior-cytokine population, but that there were other uncertainties that might push the ICER higher."*
	A further key point is the size of the patient population. It may well have been over-estimated. If Axitinib were to be approved there would effectively be two available therapies (Everolimus and Axitinib) and clinicians will need to make a rational choice. There is no direct data but there is some data to support those who did well on prior TKI doing better with a second TKI. Data presented by Rini et al (figure 3) suggest that the PFS of patients on Axitinib who have a PFS of 9 months or more do better (have	

Nominating organisation	Comment	Response
	PFS of 6.3 months compared to the overall 4.8 months for total post-Sunitinib population). Since the median PFS on sunitinib is around 9-11 months this would suggest around 50% might be “prime-candidates” for Axitinib. Ideally, this type of stratification might be assessed formally but it is often difficult as a non-commercial study as the NHS has delayed or no access to new drugs and there is no incentive for drug companies to do these studies when they are not required internationally.  Figure 3: Slide from Rini et al., ASCO GU 2012 *(See original comments from the clinical specialist for the references provided)*	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the manufacturers’ submissions and the Evidence Review Group’s critique of the manufacturer’s submission before making its recommendations.

Comments received from commentators

Commentator	Comment	Response
Commissioning Support Appraisals Service	We are in agreement with the recommendation in the ACD not to recommend axitinib for this indication as on the basis of the evidence considered it is unlikely that this treatment can be considered clinically and cost effective in real life clinical practice. • **Axitinib for this population group is not a cost effective use of NHS resources.** The ICER of £65,000 per QALY (in the subgroup who had received prior cytokine therapy) is likely to have been an over-estimate. However, other uncertainties in the economic models mean that the most plausible ICER (for both prior-cytokine and prior-sunitinib populations) is still likely to exceed £50,000 per QALY gained and could not be considered a good use of NHS resources for this population. • **A patient access scheme agreed with the Department of Health has already been taken into account in the ICER.** The size of the discount is commercial in confidence but was taken into account in the estimate of an ICER of £65,000 per QALY gained. • **Although it fulfills the criteria for a life-extending treatment for people previously treated with sunitinib, axitinib could still not be considered a good use of NHS resources for this population.** Due to value of the ICERs and the uncertainty around the ICERs. • **No trials have compared axitinib with best supportive care, which is the most appropriate and only scoped comparator for this appraisal.** There are no second-line drugs currently approved for people who have become resistant to first-line treatment and no trials have directly compared axitinib with best supportive care.	Comment noted.

Commentator	Comment	Response
	• **Axitinib improved progression-free survival, but not overall survival, compared to sorafenib in one good quality trial, but interpretation is difficult due to lack of information on appropriate comparators**. All models required indirect comparisons. Sorafenib is not approved by NICE as cost-effective for use in the NHS. The well conducted AXIS trial found that, compared to sorafenib, axitinib improved progression-free survival in people who had received prior cytokine treatment. However, there were serious limitations with the simulated treatment comparisons performed for the prior-sunitinib population; and also no comparison of axitinib with pazopanib or sunitinib for the prior-cytokine population. • **The treatment pathway for patients with advanced renal cell carcinoma is changing**. The Committee heard from experts that fewer patients now receive first-line cytokines, and that most people receive first-line treatment with pazopanib or sunitinib. The prior-pazopanib group would be a relevant population for treatment with second-line axitinib; and also pazopanib and sunitinib are available as second-line treatments for people who have received first-line cytokines. • **Axitinib has a manageable adverse effects profile compared with other treatments for advanced renal cell carcinoma.** Diarrhoea occurred in over half of patients in both arms of the AXIS trial. Hypertension, dysphonia, nausea and hypothyroidism occurred more frequently with axitinib than sorafenib.	

Comments received from members of the public

Role*	Section	Comment	Response
NHS Professional	1	Axitinib for this population group is not a cost effective use of NHS resources. The ICER of £65,000 per QALY (in the subgroup who had received prior cytokine therapy) is likely to have been an over-estimate. However, other uncertainties in the economic models mean that the most plausible ICER (for both prior-cytokine and prior-sunitinib populations) is still likely to exceed £50,000 per QALY gained and could not be considered a good use of NHS resources for this population. agree with NICE	Comment noted.
	3	There are no second-line drugs currently approved for people who have become resistant to first-line treatment and no trials have directly compared axitinib with best supportive care. Sorafenib is not approved by NICE as cost-effective for use in the NHS. The well conducted AXIS trial found that, compared to sorafenib, axitinib improved progression-free survival in people who had received prior cytokine treatment. However, there were serious limitations with the simulated treatment comparisons performed for the prior-sunitinib population; and also no comparison of axitinib with pazopanib or sunitinib for the prior-cytokine population.	Comment noted.
	4	Due to value of the ICERs and the uncertainty around the ICERs cannot be considered good use of NHS resources - even with PAS.	Comment noted.
NHS Professional	1	This is a regrettable decision on a number of counts. First, axitinib is a well-tolerated and effective TKI. Second, most patient in England at least receive everolimus second line through the CDF. For many patients, this is a more toxic and less effective agent than axitinib. The key point is that we will effectively be directed to using an equally expensive but more toxic and less effective agent for the majority of 2nd line RCC patients. I am sure this is not what the committee intends to achieve.	Comment noted. The committee's recommendations are based on both clinical and cost effectiveness evidence.

* When comments are submitted via the Institute's web site, individuals are asked to identify their role by choosing from a list as follows: 'patent', 'carer', 'general public', 'health professional (within NHS)', 'health professional (private sector)', 'healthcare industry (pharmaceutical)', 'healthcare industry'(other)', 'local government professional' or, if none of these categories apply, 'other' with a separate box to enter a description.

Role*	Section	Comment	Response
Pharmaceutical Industry	3	The manufacturer's submission presents a simulated treatment comparison (STC) between axitinib and best supportive care based on the RECORD-1 (everolimus vs. best supportive care) and AXIS (axitinib vs. sorafenib) trials. While network indirect comparisons have been recommended by NICE in the absence of head-to-head trials, these methods could not be applied for the sunitinib refractory population treated with axitinib due to lack of a suitable network of trials. Though STC attempts to address this data limitation, the STC approach lacks precedent and has significant limitations, some of which have been noted in the NICE draft response and some additional limitations that we describe below. It is stated in the MS that similar methodologies have been accepted in recent HTA appraisals to overcome gaps in the evidence network which rule out a standard indirect comparison approach, including NICE TA171 (Lenalidomide for the treatment of multiple myeloma in people who have received at least one prior therapy) and the SMC approval of everolimus in pancreatic neuroendocrine tumour. However, upon closer inspection, neither of these examples provides a precedent for acceptance of the STC methodology applied in the axitinib manufacturer's submission. Firstly, both examples were based on connected networks of trials that included a common comparator, unlike the axitinib MS. Secondly, the indirect comparison considered by the SMC evaluation of everolimus for pancreatic neuroendocrine tumors included confidence intervals for the estimated treatment differences, which are lacking from the axitinib MS. Finally, though analyses similar to STC were considered in NICE TA171 with a common comparator, the Evidence Review Group repeated the indirect comparisons using methods it considered to be more appropriate. For these reasons, we do not believe that either of these examples can be considered a precedent for acceptance of the STC methodology applied in the axitinib manufacturer's submission. The lack of confidence intervals for the STC, and inability to assess uncertainty in the results, has already been raised as a significant limitation by the ERG and in NICE's draft appraisal. We believe there are additional significant limitations with the STC analysis that would persist even if confidence intervals were derived. STC attempts to account for cross-trial differences in patient characteristics by fitting a model. It is therefore appropriate to evaluate the STC approach similarly to a multivariable regression model in an observational study.	Comment noted. Sections 4.7 and 4.8 of the FAD have been updated to reflect the Committee's discussion and conclusion regarding the STC methodology and results.

Role*	Section	Comment	Response
		From this perspective, the STC applied in the axitinib submission has significant shortcomings. Firstly, in selecting which baseline characteristics to use for adjustment, the STC approach only considers their effect on axitinib outcomes. This is insufficient for detecting important confounders, by the usual standards of epidemiological studies, because it excludes confounders that impact outcomes on everolimus and BSC but not axitinib. Furthermore, the STC analysis used p-values as the criterion to select variables for adjustment in the final model. This approach is widely-viewed as inadequate for identifying confounders in a regression model (e.g., Epidemiology: an Introduction by K. Rothmann). The MS states that the final equations were checked for their ability to replicate the source data. However, replication of source data in no way validates the selection of confounders or the ability of the model to generalize to other patient populations such as RECORD-1. For these reasons, the STC analyses do not follow generally accepted practices to adjust for confounding.	Comment noted. Sections 4.7 and 4.8 of the FAD have been updated to reflect the Committee's discussion and conclusion regarding the STC methodology and results.
	4	Given the STC's heavy reliance on MSKCC to account for cross-trial differences, it is worth noting that the MSKCC scores are defined differently in the two trials. The MSKCC score calculated in the AXIS trial substituted ECOG in place of KPS (see page 51 of the MS), which differs from direct use of KPS in the validated MSKCC score for previously treated patients (Motzer RJ, Bacik J, Schwartz LH, et al. Prognostic factors for survival in previously treated patients with metastatic renal cell carcinoma. J Clin Oncol. 2004;22:454-463) used in RECORD-1. Though this substitution may seem like a small and reasonable change, it is likely to have a substantial and biased impact on the MSKCC risk stratification. This can be seen via a simple re-analysis of the RECORD-1 data (data on file). In the original RECORD-1 trial, using the standard definition of MSKCC that includes KPS < 80% as a risk factor, the proportion of patients classified as poor prognosis was 18%. However, if the KPS threshold is changed to <= 80% the proportion with poor prognosis jumps to 39% (most KPS scores are reported as multiples of 10%), which is greater than the proportion with poor prognosis in AXIS. This change makes the KPS score threshold more comparable to the ECOG >= 1 threshold used for the non-standard MSKCC score in AXIS. This can be verified by noting that the description of KPS=80% (normal activity with some difficulty, some symptoms or signs) is much more similar to	Comment noted. Sections 4.7 and 4.8 of the FAD have been updated to reflect the Committee's discussion and conclusion regarding the STC methodology and results.

Role*	Section	Comment	Response
		ECOG=1(Symptomatic but completely ambulatory, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, for example, light housework, office work) than it is to ECOG=0 (Asymptomatic, fully active, able to carry on all pre-disease activities without restriction). Given the substantial impact of this difference in MSKCC definition, the ability of the differently defined MSKCC scores to adjust for or interpret cross trial differences between AXIS and RECORD-1 is limited. Furthermore, given the comparison of the KPS and ECOG scales, the non-standard MSKCC score used in AXIS is likely to over-estimate severity relative to the standard MSKCC score used in RECORD-1. Therefore, the adjustments for MSKCC in the STC would introduce substantial bias against everolimus. Besides the cross trial differences within the STC, the analysis incorporate selective use of external evidence. In particular, PFS data for everolimus from one source and OS data from a different source are used, rather than using both PFS and OS data from the same source. The study selected OS data from a paper by Di Lorenzo. However, it doesn't use the PFS data from either Di Lorenzo (24.1 weeks or 5.6 weeks) which is the same source as the OS data or Calvo 2012 which has PFS of the same population of sunitinib as the only prior anti-neoplastic agent as AXIS population (PFS 4.6 months). Instead it uses the PFS from Motzer 2010 which has the shortest PFS among the three (3.9 months). No justification is given for use of the different sources of evidence. In addition, while no data are available from RECORD-1 to estimate the mean, and only the median is available for everolimus, the STC extrapolates a mean PFS and OS for everolimus based on assumptions; and reports mean differences in PFS and OS that are larger than the medians, and that favor axitinib. These selective modeling decisions compound the uncertainty in the comparative clinical and cost-effectiveness derived from the STC. It is also noteworthy that the OS results in the STC were not adjusted for post progression treatment differences. On the basis of the STC, it has been projected that patients receiving treatment with axitinib would achieve (better) PFS benefit (8.3 months) than those receiving everolimus (4.6 months). The cost effectiveness results presented to NICE are based on this inference. However, the analysis does not account for substantial differences in the availability and use of other therapies post progression with everolimus vs. axitinib. As the data from two trials show, patients in the AXIS trial had access to more treatments post progression and almost	Comment noted. Sections 4.7 and 4.8 of the FAD have been updated to reflect the Committee's discussion and conclusion regarding the STC methodology and results.

Role*	Section	Comment	Response
		half of the patients used them. In the RECORD-1 trial, about one third used any treatments post progression. It would be misleading to conclude that any overall survival difference between axitinib and everolimus is solely attributable to the efficacy of axitinib.	