NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Health Technology Appraisal

Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma

Response to consultee, commentator and public comments on the second Appraisal Consultation Document (ACD2)

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 patient/carers and professionals can nominate clinical specialists and patient experts to present their personal views to the Appraisal Committee. Where clinical specialists and patient experts make comments on the ACD separately from the organisations that nominated them, these are presented alongside the consultee comments in the tables below.

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
Bayer Healthcare	Thank you for the opportunity to respond to the second appraisal consultation document (ACD) containing recommendations for Nexavar for the treatment of renal cell carcinoma. We are disappointed that NICE have been unable to recommend Nexavar as a treatment post immunotherapy, despite the Committee recognising it as a clinically effective therapy with robust data in a group of patients for whom there are no other treatment options available. Please find below Bayer's response to the ACD. These are based on both requested general headings as well as a section outlining factual issues contained within the document.	Comment noted. See detailed responses below.
Bayer Healthcare	**Factual issues** Nexavar is indicated for the treatment of patients with advanced renal cell carcinoma who have failed prior interferon-alpha or interleukin-2 based therapy or are considered unsuitable for such therapy. Section 3.2.1 incorrectly states that the "condition has failed to respond to" immunotherapy; patients may have responded initially to such therapy, but consequently failed. This statement is also included throughout the document when referring to the indication and treatment line setting of Nexavar (e.g. 4.2.8, 4.1.20, 4.2.10, 4.3.2).	Comment noted. This has been amended accordingly throughout the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Bayer Healthcare	We can confirm that the price of Nexavar is now £2,980.47. Please can you update Section 3.2.3 so that it no longer discusses the previous price of £2504.60, and update 4.2.10 so that it does not refer to "the new price" but rather "the price".	Comment noted. This has been amended in the FAD, see section 3.2.3 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.

Consultee	Comment	Response
Bayer Healthcare	The list price of temsirolimus has not been included in Section 3.4.1 although the list price has been available for several months. Although it is not currently listed in the BNF (edition 56), it is currently listed by MIMs (February 2009) as £620.00 for a 1.2ml vial (25mg/ml concentrate). In section 4.2.21 you refer to having confirmed the price with the BNF.	Comment noted. This has been amended in the FAD, see section 3.4.3 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Bayer Healthcare	The survival findings reported in 4.1.16 refer to the first interim analysis. Please can you update this section to reflect this.	Comment noted. This has been amended in the FAD, see section 4.1.16 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Bayer Healthcare	The updated analysis on progression free survival (PFS) was undertaken at crossover rather than before crossover occurred (section 4.1.17). The median PFS values shown and statements made are only partly correct. Escudier et al. (2007) report the following: ➢ Independent assessment (pre planned, Jan 2005) – 2.8m vs 5.5m (HR 0.44; 95% CI 0.35 to 0.55) ➢ Investigator assessment (pre planned, Jan 2005) – 2.8m, vs 5.9m (HR 0.44; 95% CI 0.35 to 0.44) ➢ Investigator assessment (at crossover, May 2005) – 2.8m vs. 5.5m (HR 0.51; 95% CI 0.43 to 0.60) Please can you update the section to reflect this.	Comment noted. This has been amended for pre-planned independent assessment and investigator assessment but it was noted that in the Escudier paper that no HR or CI were reported for the pre-planned investigator assessment, see section 4.1.17 in the FAD ' bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.

Consultee	Comment	Response
Bayer Healthcare	The statistical significance referred to in 4.1.18 refers to both partial response and stable disease, although it only refers to those with a partial response. The number (percentage) with stable disease was 333 (74%) and 239 (53%) for the Nexavar and placebo group, respectively.[1]	Comment noted. This has been amended in the FAD, see section 4.1.18 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Bayer Healthcare	The Committee concluded that the prior cytokine sub group was not pre-specified (Section 4.3.19) Although this is not stated in the TARGET publication (Escudier et al. 2007), we can confirm, as previously stated, that this and other sub-groups analysed were pre-planned.	Comment noted. This has been amended in the FAD, see section 4.3.20 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Bayer Healthcare	In Section 4.3.19, it states that the Committee "was aware that some of the participants in the 'no prior cytokine' subgroup in the trial [TARGET] would have received sunitinib as a first-line treatment". The exclusion criteria for the clinical trial, TARGET, included patients who had any prior medicines that are licensed or investigational that target VEGF and VEGF receptors (for example, sunitinib).	Comment noted. This has been amended in the FAD, see section 4.3.27 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.

Consultee	Comment	Response
Bayer Healthcare	The health related quality of life section (4.1.19) refers to a 30 week treatment period. This should be 32 weeks (the first four cycles were 6 weeks long, the 5th cycle 8 weeks long). The same section also refers to a significantly greater number of adverse events experienced in the Nexavar arm. The paper on which this section is based (Bukowski et al. 2007) does not report either this or the adverse events that you report.[2] The statistical significance of $p<0.0001$ refers to "bothersome side effects of treatments" rather than actual adverse events. The paper then concludes that Nexavar appeared "to have no impact on energy, fatigue, quality of sleep, pain, or weight change, items that may be negatively impacted by cancer treatment" which have not been mentioned in this section of the ACD.	Comment noted. This has been amended in the FAD, see section 4.1.19 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Bayer Healthcare	The ACD recommends that further research on the impact of Nexavar on health related quality of life (HRQoL) should be undertaken (Section 6.2). However, from the Committee's appraisal of Nexavar under the end of life criteria, the Committee believe that the additional HRQoL required would be too great to fall within the current threshold range (4.3.21). If the Committee's argument is correct, there would therefore be no point in NICE recommending further HRQoL studies for Nexavar.	Comment noted. This has been amended in the FAD accordingly, see section 6.2 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.

Consultee	Comment	Response
Bayer Healthcare	**Interpretation of clinical and cost-effectiveness** The Committee expressed concern about the difference in the ICER for the prior cytokine group in the original analysis and resubmission (Section 4.3.19). Furthermore, in Section 4.2.30, the ACD states the DSU observations on our revised ICER, concluding "that no explanation for this [change in results] was provided by the manufacturer". However, the reason for this should have been self-explanatory to the DSU – namely that the modelling approach was changed to that adopted by PenTAG, utility values and costs were changed to reflect those preferred by PenTAG and that a considerably more complete dataset for the prior cytokine group was provided in the resubmission compared to the original analysis. Furthermore, the assumption of proportional hazard was shown to not hold (see Section 4.2.31), which also resulted in a marked difference in the ICER estimated for the overall group by PenTAG themselves (shown at the public part of the 14th Jan 2009 Committee meeting). Many of these reasons were explained to the Committee by PenTAG in the public part of the Committee meeting (14th Jan 2009) and some of these reasons are also highlighted in the ACD (Section 4.2.10). Please can you update the relevant sections (e.g. 4.2.30, 4.3.19) to reflect the reason why the ICERs changed for not only our own estimates, but those by the academic group.	Comment noted. This has been amended in the FAD. See sections 4.2.32, 4.2.33, 4.3.20 and 4.3.25 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.

Consultee	Comment	Response
Bayer Healthcare	**Has all relevant evidence been taken into account** Based upon the Phase III trial, TARGET,[1] the Committee "concluded that, as the data were limited, sorafenib as a first-line treatment for those unsuitable for immunotherapy with advanced and/or metastatic RCC could not be considered to be clinically effective" (Section 4.3.15). There are relatively low patient numbers in the Phase III trial for patients who are unsuitable for immunotherapy. However, as provided in the original submission in January 2008, two large, expanded access programmes of Nexavar in a real world setting within Europe and North America both included patients who were ineligible for immunotherapy.[3, 4] In the North America programme, 224 patients who had Nexavar as first line treatment and were evaluated in the extension protocol had a median PFS of 35.1 weeks (8.1 months).[5, 6 1] In the European expanded access programme, 28% of patients (n=318) were unsuitable for cytokine therapy. The median PFS for these patients was 6.0 months.[7] These data demonstrate that Nexavar is a clinically effective option in this patient group, as recognised by the EMEA when the indication was approved.	Comment noted. The details of the expanded access programmes were considered by the Committee. The Committee noted that the data came from single-arm studies and were available only in abstract form and so sorafenib was not considered clinically effective in this group of patients. See the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma', sections 4.1.13 and 4.3.16.
Bayer Healthcare	**Suitability of the provisional recommendation** Bayer supports that clinicians should have a range of treatments available for their patients, choosing the pathway which they believe will be in the best interest of the patient presenting to them. There is limited clinical evidence on sequencing available in the UK metastatic and/or advanced RCC population due to low uptake of the treatments under consideration to date. However, Nexavar still provides a clinically effective treatment post immunotherapy, and our exploratory analysis, based on estimations and/or assumptions from the academic group themselves, does indicate that immunotherapy followed by Nexavar is a clinically relevant option to clinicians, and may also offer savings to the NHS overall. The importance of clinician choice is particularly acute when specific patient groups are considered (see next section).	Comment noted. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.22.

[1] In total there were 1247 (out of 2502) patients who received Nexavar as a first line therapy. As the US license was granted earlier than expected, at which point enrolment stopped, 224 first line patients were evaluated within the extension protocol to estimate median PFS.

Consultee	Comment	Response
Bayer Healthcare	**Equality related issues** Not all advanced RCC patients will be suitable for sunitinib based on the guidance in the FAD (e.g. poor performance status and/or are cytokine unsuitable). The current recommendations proposed throughout the overall MTA, including the first line recommendation for sunitinib, have important equality issues for four specific sub-groups of patients.	Comment noted. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.18, 4.3.25, 4.3.26 and 4.3.28.
Bayer Healthcare	Patients who are unsuitable for immunotherapy will only be allowed to receive best supportive care i.e. they cannot benefit from any of the new technologies, including sunitinib. Nexavar is indicated for this patient group, having demonstrated clinical benefit. We have highlighted the main clinical evidence supporting Nexavar in this patient group in the section "Has all relevant evidence been taken into account". Possible reasons that a patient may be considered unsuitable for immunotherapy includes clinically significant organ impairment, low likelihood of response to therapy, presence of hepatic metastases, two or more metastatic organ sites, and contraindications such as liver dysfunction or brain metastases.[8, 9]	Comment noted. See detailed response above.
Bayer Healthcare	Patients who may be suitable for immunotherapy but not sunitinib. Potential patient groups who may be less suitable for sunitinib include those with congestive heart failure, poor nutritional state and impaired mobility;[10] it should also be noted that patients with hypertension or clinically significant cardiovascular events were excluded from the sunitinib Phase II trial.[211] These patients will only be able to receive the less effective immunotherapy as a first line treatment and consequently will not benefit from any of the new treatments, although Nexavar has demonstrated to the Committee that it is a clinically-effective treatment after immunotherapy.[11]	Comment noted. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.22 and 4.3.28.
Bayer Healthcare	Those patients who may rapidly progress (or not respond) on sunitinib, but would benefit from a subsequent treatment. Based on the progression free survival curve from the Phase III trial against interferon, approximately 10% on sunitinib had progressed within one month.	Comment noted. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.27.

[2] In the Phase II trial for Nexavar, TARGET, patients with hypertension were not excluded.[1]

Consultee	Comment	Response
Bayer Healthcare	Those patients who do not continue on sunitinib due to tolerability issues. Section 4.1.8 of the sunitinib FAD concluded that 8% of patients on sunitinib discontinued in the trial due to adverse events as well as acknowledging the emerging concerns in the published literature about the frequency of cardiovascular events associated with sunitinib. Khakoo et al. (2008) found that average time of symptomatic onset of heart failure associated with sunitinib occurred within 22 days of initiation in patients who developed symptomatic cardiac dysfunction without any other obvious cause.[12]	Comment noted. See response above.
Bayer Healthcare	For those patients who are unfortunate enough not to be able to benefit from sunitinib, Nexavar can offer a clinically relevant treatment option,[7, 13-17] as long as they are not contraindicated and are unsuitable for immunotherapy. Immunotherapy after a tyrosine kinase inhibitor (TKI) should be used with caution due to tolerability issues.[18] Sablin et al. (2007) has shown that there appears to be a lack of cross resistance between Nexavar and sunitinib.[15] Furthermore, the evidence of effect of Nexavar post sunitinib has been demonstrated, with a median PFS of patients of between 4 and 5 months,[7, 14] despite such patients likely to be in a poorer performance status than the general advanced RCC population.[7] The use of Nexavar post sunitinib was also confirmed by the clinical expert at the Committee meeting (public part, 14th Jan 2009) as being a potential clinical option especially where there are tolerability issues related with sunitinib; clinical experience of Nexavar and sunitinib has shown that toxicities experienced with the two therapies are different,[16, 19] allowing clinicians to take these factors into account when recommending subsequent therapies for patients.	Comment noted. See response above.
Bayer Healthcare	**Conclusion** In the FAD, the Committee acknowledged that sunitinib should, along with current practice, immunotherapy, be available as treatment options for clinicians. Whilst sunitinib has demonstrated clinical benefit over immunotherapy in those patients who are suitable for immunotherapy, there does remain a group of patients for whom sunitinib or immunotherapy provides no or limited benefit, or for whom sunitinib is less suitable. These are those unsuitable for immunotherapy and/or sunitinib and those patients who commence sunitinib but withdraw due to cardiovascular toxicity reasons or because they do not respond. For these patients, the current ACD recommendations mean that these unfortunate patients will not be able to benefit from any other active treatment such as Nexavar.	Comment noted. See responses above.

Consultee	Comment	Response
Bayer Healthcare	We would like the Committee to take into consideration the information provided within this letter in making a final recommendation on Nexavar. In particular, we ask that special consideration is given to the clinical benefit of Nexavar in both the immunotherapy unsuitable patient group and post sunitinib patient group, and, most importantly, the equality implications for the four patient groups from the Committee's provisional recommendations. When making their recommendation, we believe the Committee should evaluate these four patient groups under the end of life criteria, acknowledging that they represent a small patient group who, based on current clinical practice and recommendations by the Committee, have no other treatments available to them except best supportive care, and for whom Nexavar can provide a substantial clinical benefit.	Comment noted. See responses above.
Roche Products	Thank you for sending us the Appraisal Consultation Document (ACD) for the above technology appraisal. Roche welcomes the acceptance by the Appraisal Committee at its last meeting of a number of key points of feedback which were made regarding the economic modelling for bevacizumab which has resulted in a revised ICER of approximately £82,700.	Comment noted. No actions required.
Roche Products	In the light of this position, Roche has proposed a Patient Access Scheme in order to further reduce this base case ICER to a level which can be considered as being cost effective. Ministers have given permission for this Scheme, which was submitted to NICE in advance of this ACD response on 1st March, to be evaluated as part of the ongoing appraisal.	Comment noted. The patient access scheme was agreed by the Department of Health in time for the fourth Committee meeting and was considered fully by the Committee. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 3.1.3.
Roche Products	Alongside the evaluation of the tabled Patient Access Scheme, there are two important points which the Committee needs to consider at its next meeting. These are: 1. The tolerability profile of the combination of bevacizumab and interferon (IFN) which appears to have been particularly focussed upon by the Committee at its last meeting; and 2. The application of the End of Life criteria (EoLC) to bevacizumab.	Comment noted. See detailed responses below.

Consultee	Comment	Response
Roche Products	Roche was surprised that in the consideration of the end-of-life criteria in relation to bevacizumab, particular emphasis appeared to be uniquely placed on the combination of bevacizumab plus IFN being poorly tolerated as one reason for rejecting the applicability of the end of life criteria. This appears to us to be arbitrary and unreasonable particularly because adverse events have already been taken into account in the costs and benefits calculations used to generate the ICER. We deal with this issue further in our main response below.	Comment noted. See detailed responses below.
Roche Products	It can perhaps be inferred from the positive recommendation already given for sunitinib that the Committee believe that bevacizumab plus IFN is significantly less well tolerated than sunitinib. We describe below the empirical evidence which suggests that overall the tolerability of bevacizumab plus IFN appears at least no worse than that of sunitinib. This is based on a review of safety datasets that are comparable in terms of treatment duration and which were included in our original submission. We would also point out that the Committee appear to have considered safety analysis from an immature dataset (at 6 months median treatment duration) whilst considering a more mature dataset for efficacy.	Comment noted. The Committee noted that there were a number of patient concerns associated with taking IFN and that bevacizumab is only licensed for use in combination with IFN. The Committee also noted that the costs of the adverse effects had been taken into account, but that any disutility associated bevacizumab or IFN treatment had not been taken into account. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.5 and 4.3.8.
Roche Products	The ACD suggests that the Committee accepted that three out of the four end-of-life criteria should apply to bevacizumab, apart from the small patient population criterion. Roche believes that, as for sunitinib, this criterion should also apply positively to bevacizumab and we put forward argumentation to support this position in our response below.	Comment noted. See response below.

Consultee	Comment	Response
Roche Products	In summary, Roche considers that the combination of bevacizumab plus IFN - when considered in the context of the Patient Access Scheme approved by Ministers for evaluation by NICE as part of this appraisal – can now be regarded as being clinically and cost effective. The combination of bevacizumab and IFN provides similar efficacy benefits as sunitinib in the first line setting, and in accordance with the above conclusions appears to have a similar frequency of adverse events, albeit with a very different toxicity profile.	Comment noted. The Committee was not persuaded that bevacizumab plus IFN met all of the criteria for fulfilling the life-extending, end-of-life treatment. See the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.9.
Roche Products	With similar cost effectiveness to sunitinib in the context of the proposed Patient Access Scheme, we believe that bevacizumab plus IFN should be recommended for use by the Committee to provide NHS cancer patients with a choice of treatment options which is supported by the patient choice agenda set out in England's Cancer Reform Strategy.	The recommendations are not inconsistent with the NHS cancer plan. The NHS cancer plan pledges to make the most appropriate treatment available to patients, and specifically refers to NICE guidance and therefore the concept of using cost-effectiveness as a criterion for decision making.
Roche Products	<u>Avastin Patient Access Scheme (APAS)</u> Roche welcomes the acceptance by the Appraisal Committee at its last meeting of a number of key points of feedback which were made regarding the economic modelling for bevacizumab which has resulted in a revised ICER of approximately £82,700. Roche has proposed a patient access scheme (PAS), which further reduces this ICER we believe to a level which can be regarded as being cost effective and indeed in line with the cost effectiveness estimates for first-line sunitinib use (approximately £54,000). Under the PAS any bevacizumab that a patient receives beyond a cumulative dose of 10g in any treatment year will be rebated. Additionally the drug acquisition cost of all IFN used for each patient will be reimbursed. We submitted details of this scheme to NICE on 1st March for evaluation.	Comment noted. The patient access scheme was agreed by the Department of Health in time for the fourth Committee meeting and was considered fully by the Committee. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 3.1.3.

Consultee	Comment	Response
Roche Products	<u>Adverse-Event profile of bevacizumab + IFN</u> In several sections throughout the ACD, the Committee has made reference to the adverse event profile of the combination of bevacizumab and IFN as follows: Section 4.3.5 *The Committee was persuaded that bevacizumab plus IFN-α is a clinically effective first-line treatment. However, it was mindful of the adverse effects associated with the combination of bevacizumab and IFN-α* Section 4.3.7 *'it noted there were more participants in the bevacizumab arm of the trial than the IFN-α arm that were censored. The Committee considered that this was likely to be caused by a greater number of participants withdrawing from bevacizumab plus IFN-α treatment than IFN-α plus placebo treatment, which could be because of adverse effects of bevacizumab plus IFN-α treatment '* Section 4.3.8 The Appraisal Committee appear, in part, to presently base the guidance for bevacizumab and IFN on the opinion of patients who had commented on the appraisal: *'and its use in combination with a drug that is reported by patients to have substantial adverse effects,'* Whilst we fully acknowledge the importance of public comment on appraisals, such comments need to be placed into context and interpreted alongside the empirical data from RCTs. We have submitted robust clinical trial data from a randomised, double-blind, placebo controlled study and believe that any appraisal of the tolerability of this combination should be based primarily upon this clinical dataset.	The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators and the public in response to the Assessment report and the Appraisal Consultation Document. The adverse event profile of bevacizumab plus IFN-α was not considered in the context of the end-of-life criteria. See section 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Roche Products	We were surprised by the Committee's focus on the tolerability profile of bevacizumab and IFN, which we would like to revisit through review of the data submitted from the pivotal study AVOREN (Escudier et al., 2007).	Comment noted. See response below.

<table>
<tr><th>Consultee</th><th>Comment</th><th>Response</th></tr>
<tr><td>Roche Products</td><td>As can be seen from the table below, patients were on study drug significantly longer in the bevacizumab plus IFN arm (median 9.7 months) compared to the IFN plus placebo arm (median 5.1 months). It is also important to note that patients also received IFN for longer in the bevacizumab combination arm, compared to IFN alone.
<table>
<tr><th></th><th>IFN + placebo (n=304)</th><th>Bevacizumab + IFN (n=337)</th></tr>
<tr><td>Median duration of treatment, mo (range)</td><td></td><td></td></tr>
<tr><td>Bevacizumab/placebo</td><td>5.1 (0-24)</td><td>9.7 ((0-24.4)</td></tr>
<tr><td>IFN</td><td>4.6 (0.2-12.6)</td><td>7.8 (0.2-12.6)</td></tr>
</table>
As can be seen from Table 1 (Appendix A), there was a similar proportion of patients who experienced adverse events in both arms of AVOREN. There were more grade ≥3 adverse events reported in the bevacizumab arm (203 for bevacizumab plus IFN vs 137 for IFN alone) and more patients in the bevacizumab + IFN arm withdrew due to adverse events compared to IFN alone (28% vs 12%, respectively). However this variance between the arms can be explained by the fact that patients were on the study treatment for almost twice as long in the bevacizumab arm. This observation is supported by the comparison of the safety data from longer follow-up of the sunitinib pivotal study, versus the less mature dataset presently considered by the Committee (Table 2, Appendix A). Whilst the incidence of adverse events changes little in the IFN arm, considerable difference in the incidence of sunitinib associated adverse events were observed as the median treatment duration increased.</td><td>Comment noted. The Committee noted that participants in the bevacizumab plus IFN arm in the trial had received treatment for almost twice as long as those in the IFN alone arm. See FAD ‘bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma’ section 4.3.7.</td></tr>
</table>

Consultee	Comment	Response
Roche Products	Since sunitinib has received positive NICE guidance, within the same MTA, it seems pertinent to compare the adverse event profile for sunitinib with that of bevacizumab + IFN. Unlike the AVOREN study, the sunitinib pivotal study (Motzer et al., 2007) had an open label study design, whereby both patients and investigators were aware of which study drug the patient was receiving, and as such any subjective measures may have been impacted by inherent bias. For example, 15 patients (4%) randomised to the IFN arm withdrew consent prior to receiving study drug, versus none in the sunitinib arm. Given that sunitinib at that time was the 'new /innovative therapy' with promising efficacy data from phase II studies, it is not surprising that patients chose not to participate in a study once they learned that they would receive an 'older / less effective' drug. Similarly, following publication of the second interim analysis, 25 patients who were receiving IFN and whose disease had not progressed switched to the sunitinib arm. These observations indicate how patient preference can potentially impact study outcomes in an open label setting. With regard to the adverse event profile for sunitinib, the Committee concluded in Section 4.1.12. of the sunitinib FAD that '*The frequency of adverse events associated with sunitinib is comparable to that associated with IFN-α monotherapy.'* As mentioned earlier, the Committee has based it's findings on the adverse event profile of sunitinib on an immature dataset, first presented at ASCO in 2006 and later published in 2007 (Motzer et al., 2007). At the time of this second interim analysis, the median duration of treatment was 6 months (range, 1 to 15) in the sunitinib group, and 66% of patients remained on treatment. However, by the third interim analysis (Motzer et al., 2007b), the median treatment duration had almost doubled to 11 months, better reflecting the efficacy of sunitinib with a median PFS of 11 months. At this data cut, only 27% of patients remained on therapy, and therefore the full safety profile for the majority of patients had been captured. This dataset was included in our submission for bevacizumab and IFN, as part of the indirect comparison with sunitinib. A further update relating to final analysis of overall survival (submitted by Pfizer as part of this MTA) was presented in September 2008 (Negrier et al., 2008).	Comment noted. The Committee heard from clinical experts and people with RCC that immunotherapy is associated with high toxicity, is poorly tolerated and is administered by subcutaneous injection. See sections 4.3.2, 4.3.5 and 4.3.8 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'. The adverse event profile of bevacizumab plus IFN-α was not considered in the context of the end-of-life criteria. See section 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.

Consultee	Comment	Response
~~Roche Products~~	~~With regard to the adverse event profile for sunitinib, the Committee concluded in Section 4.1.12. of the sunitinib FAD that '*The frequency of adverse events associated with sunitinib is comparable to that associated with IFN-α monotherapy.*' As mentioned earlier, the Committee has based it's findings on the adverse event profile of sunitinib on an immature dataset, first presented at ASCO in 2006 and later published in 2007 (Motzer et al., 2007). At the time of this second interim analysis, the median duration of treatment was 6 months (range, 1 to 15) in the sunitinib group, and 66% of patients remained on treatment. However, by the third interim analysis (Motzer et al., 2007b), the median treatment duration had almost doubled to 11 months, better reflecting the efficacy of sunitinib with a median PFS of 11 months. At this data cut, only 27% of patients remained on therapy, and therefore the full safety profile for the majority of patients had been captured.~~ ~~This dataset was included in our submission for bevacizumab and IFN, as part of the indirect comparison with sunitinib. A further update relating to final analysis of overall survival (submitted by Pfizer as part of this MTA) was presented in September 2008 (Negrier et al., 2008).~~	
Roche Products	The reported safety data from all of three analyses are summarised in Table 2 (Appendix A) for ease of comparison and any differences should be considered in the context of different treatment duration and proportion of patients still on therapy (i.e. patients whose disease had not progressed). Given that the median duration of sunitinib is considerably longer in the third interim analysis, the increased incidence of sunitinib adverse events was not unexpected. Patients in the sunitinib arm experienced significantly more grade≥3: diarrhoea, nausea, vomiting, hypertension, hypothyroidism, neutropenia, thrombocytopenia, and hyperlipidaemia; whereas patients in the IFN arm experienced more grade≥3 lymphopaenia ($p<0.05$ for all comparis ons). As such, when reviewing the safety dataset most relevant to the efficacy outcomes reported for sunitinib and given the very distinct toxicity profiles of the two agents, it appears that sunitinib is at best no less toxic than IFN.	Comment noted. See response above.

Consultee	Comment	Response
Roche Products	Whilst acknowledging the inherent issues with indirect comparisons of data from independent clinical trials, we believe it is important to compare the tolerability profiles of bevacizumab + IFN vs sunitinib given the different guidance issued for the two technologies. Safety data from the AVOREN study is compared with the most relevant dataset from the sunitinib pivotal study in terms of treatment duration (i.e. the third interim analysis) in Table 3, which was also included in our original submission for this MTA. Overall, the tolerability of bevacizumab + IFN appears at least no worse than that of sunitinib.	As well as the clinical evidence, the Committee heard from clinical experts and people with RCC that immunotherapy is associated with high toxicity, is poorly tolerated and is administered by subcutaneous injection. See the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.2, 4.3.5 and 4.3.8.
Roche Products	Finally, we would like to remind the Committee of the IFN dose reduction analysis that formed part of the original submission for bevacizumab and IFN. Given the wealth of experience with IFN in the treatment of advanced RCC patients, an algorithm reflecting standard clinical practice of IFN dose reductions for the management of IFN-related toxicity was included in the AVOREN protocol (Melichar et al., 2007, 2008). Approximately 40% of patient in the bevacizumab plus IFN arm reduced the dose of IFN, compared to 30% in the IFN plus placebo arm. (As expected, dose reduction resulted in decreased side effects in both groups, and interestingly the bevacizumab + reduced dose IFN demonstrated similar efficacy to the ITT study group. Thus, the AVOREN study showed that IFN side effects can be effectively managed through a standard dose reduction algorithm, without compromising efficacy. It is also interesting to note 27% patients had IFN dose reductions in the sunitinib pivotal study, whereas 50% of patients on in sunitinib had dose reductions due to adverse events (Negrier et al., 2008). Once again, when comparing the amount of dose reduction required to manage adverse events in the two pivotal studies, bevacizumab + IFN appears at least no worse than sunitinib.	As well as the clinical evidence, the Committee heard from clinical experts and people with RCC that immunotherapy is associated with high toxicity, is poorly tolerated and is administered by subcutaneous injection. See the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.2, 4.3.5 and 4.3.8.

Consultee	Comment	Response
Roche Products	*Conclusion* In summary, we believe that robust RCT data from the AVOREN study demonstrates that the tolerability profile of bevacizumab + IFN is acceptable, in the context of the significant efficacy benefits the combination provides over IFN alone. Therefore, we believe the Committee's particular focus on this issue is not substantiated by the data and is inappropriate. Moreover, review of the pivotal data for sunitinib suggests that it is at best no less toxic than IFN, and indirect comparison of the safety data for the two technologies does not suggest that sunitinib is any more tolerable than bevacizumab + IFN. Hence we believe that the Committee has been inconsistent in this regard in it's appraisal of the two technologies side by side.	Comments noted. See detailed responses above.
Roche Products	Application of End of Life Criteria (EoLC) Whilst we accept that the Appraisal Committee has tested the application of the end of life criteria on only a limited number of occasions so far since the Supplementary Advice was issued, it appears that bevacizumab has on this occasion been treated differently to other drugs. The ACD indicates that the Appraisal Committee accepted that three of the four EoLC did apply to the combination of bevacizumab and IFN for this technology appraisal and we agree with the position of the Committee regarding the applicability of the first three criteria:	Comment noted. See detailed responses below.
Roche Products	*2.1.1* ***The treatment is indicated for patients with a short life expectancy, normally less than 24 months*** *"The Committee noted from the clinical trials that life expectancy with IFN-α treatment alone was unlikely to be greater than 24 months and was potentially as low as 12 months."*	Comment noted. No actions required.
Roche Products	*2.1.2* ***There is sufficient evidence to indicate that the treatment offers an extension to life, normally of at least an additional 3 months, compared to current NHS treatment*** *"The Committee considered that even though the median overall survival in the bevacizumab arm of the trial had not been reached, the Committee considered that it was likely that bevacizumab plus IFN-α would increase overall survival by more than 3 months in comparison with IFN-α alone."*	Comment noted. No actions required.
Roche Products	*2.1.3* ***No alternative treatment with comparable benefits is available through the NHS*** The Appraisal Committee *"..had heard that RCC does not respond well to IFN-α and that bevacizumab represents an improvement in the treatment of advanced and/or metastatic RCC."*	Comment noted. No actions required.

Consultee	Comment	Response
Roche Products	However, in relation to the last criteria we disagree with the Committee's position: *2.1.4* *The treatment is licensed or otherwise indicated, for small patient populations.* *In summary , the Committee was not persuaded that bevacizumab plus IFN-α meets all the criteria, particularly given the size of the patient populations (in RCC and other cancers) for whom it is licensed and its use in combination with a drug that is reported by patients to have substantial adverse effects,..'*	Comment noted. See detailed responses below.
Roche Products	*Adverse Events* It is not clear to Roche why the adverse event profile of bevacizumab and IFN has been raised as a consideration under the End of Life Criteria. The End of Life Criteria Supplementary Advice does NICE direct Committees to examine this issue. Furthermore, as demonstrated above, the adverse event profile for the combination of bevacizumab and IFN is no worse than that observed for sunitinib. This is supported by the data from the randomised clinical trial of sunitinib versus IFN, which the Committee acknowledged. There is no mention of the adverse event profile for sunitinib in the Committee's consideration of End of Life criteria in the corresponding FAD for sunitinib.	Comment noted. Adverse effects are not considered in the End of Life Criteria, see section 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma',
Roche Products	*"Small Population" Criterion* Generally, .the inclusion of this particular criterion in the end-of-life supplementary advice is particularly challenging, not least because of the absence of empirical evidence to suggest that society places any greater value on treating individuals with rare diseases over those with common ones.	Comment noted. The Committee considered this. See sections 4.3.4 and 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Roche Products	However, we offer up the following points in support of arguing that this criteria should be applied positively to bevacizumab in this appraisal as it has been for sunitinib: **Reimbursement status** Whilst bevacizumab may be licensed for the treatment of multiple cancer indications it is currently not reimbursed for any indication on the NHS. If recommended for use in this appraisal for renal cell cancer, this would effectively be the first ever indication used in the NHS. There has to date been no recovery of the development costs of bevacizumab whatsoever from any use on the NHS.	Comment noted. The Committee considered this. See section 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.

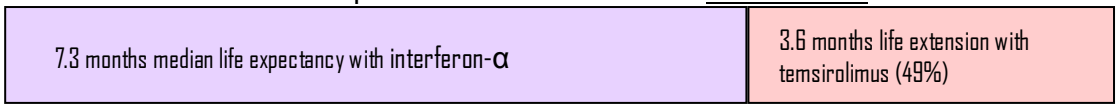
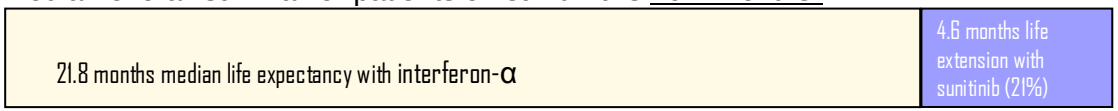
Consultee	Comment	Response
Roche Products	There are a number of further issues with including indications outside of the scope of the appraisal when determining the size of the population of interest including: Scope of appraisal Since the scope of this appraisal is to investigate the clinical and cost effectiveness of treatments for RCC, it seems unreasonable to base any case for endorsement at least in part on the regulatory status of other indications which are not relevant and outside the scope of the appraisal. This would seem unfair to renal cell cancer patients.	Comment noted. The Committee considered this. See section 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Roche Products	First come, first served It also seems unreasonable to potentially disadvantage renal cell cancer patients on the basis of the order and sequence within which marketing authorisations happen to be granted for other particular indications (in this case comparing for example the sunitinib licencing sequence with that of the bevacizumab licencing sequence).	Comment noted. The Committee considered this. See section 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Roche Products	Specific development costs Finally, follow-on indications require the full range of clinical trials to establish safety and efficacy. Development costs are unique to each particular indication and need to be considered as such. We therefore believe that the regimen being appraised in this setting should be considered in isolation in establishing the relevant patient population. In summary, we believe that since the number of renal cell cancer patients is within acceptable 'small population' limits (less than 4,000) that the fourth small population criterion should on this occasion equally apply positively to both bevacizumab and sunitinib alike.	Comment noted. The Committee considered this. See section 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Roche Products	Roche considers that the application of the end of life criteria within this appraisal may result in equality issues for renal cell cancer patients who may be disadvantaged if the end of life criteria within this MTA are applied inconsistently or due for example to factors outside of the particular scope of the appraisal such as sequencing of marketing authorisation applications being taken into account in decision making. We hope this feedback is useful to support the further deliberations of the Committee.	Comment noted. See detailed responses above.
Wyeth	Wyeth consider that there are equality related issues with regards to patients eligible for treatment with temsirolimus that need special consideration within this appraisal and as a consequence the provisional recommendations of the Appraisal Committee are not sound and do not constitute a suitable basis for the preparation of guidance to the NHS.	Comment noted. See detailed responses below.

Consultee	Comment	Response
Wyeth	Failure to adequately address the very small number of patients eligible for treatment, and their degree of clinical need, when making judgements on the acceptability of temsirolimus, based on the incremental cost effectiveness ratio (ICER) and the application of the supplementary advice when appraising life-extending, end of life treatments has resulted in discrimination against advanced renal cell carcinoma patients (aRCC) with poor prognosis. Temsirolimus remains the only technology evaluated in this appraisal to demonstrate a significant improvement in the overall survival of aRCC patients compared to interferon-α, the current standard of care within the NHS. Furthermore, temsirolimus is **the only technology demonstrating efficacy in poor prognosis patients**.	Comment noted. The Committee noted that the only current standard treatment is immunotherapy that there is an unmet clinical need, particularly so for people with a poor prognosis. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.2. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that temsirolimus for the treatment of advanced and/or metastatic RCC for people with a poor prognosis would not be a cost-effective use of NHS resources. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.15.

Consultee	Comment	Response
Wyeth	**Appraisal Committee's preliminary recommendations** Wyeth welcomes the proposed recommendation of one of the four drugs (sunitinib) for patients with a good performance status. However, as identified in the FAD, this treatment is not suitable aRCC patients with poor prognosis (at least 3 of 6 prognostic risk factors) due to lack of evidence of efficacy. Moreover, as the ACD currently stands these poor prognosis patients will be denied access to temsirolimus - the only available innovative treatment with proven clinical effectiveness.	Comment noted. See response above.
Wyeth	Wyeth is disappointed and concerned that this group of aRCC patients with poor prognosis are being denied access to an effective treatment that has been proven to increase overall survival. Albeit a 'very small group of patients' (as described in paragraph 4.3.12 of the ACD) this recommendation fails patients which Wyeth feels is discriminatory. We estimate that only about 238 patients in England would be eligible for treatment with temsirolimus annually and the overall drug cost to the NHS would therefore be less than £4 million per year. In return, treatment with temsirolimus adds another 3.6 months to a life expectancy of about 7 months, compared to treatment with current standard of care, interferon-α – a 50% extension to life that is particularly invaluable both for patients and for their families when time is so limited by the extent of disease at diagnosis, prior to treatment.	The Committee considered that use of temsirolimus, given the estimated ICERs under consideration, would not be an efficient use of NHS resources and would be likely to displace activity of greater overall benefit to other, unknown groups of people, some of whom may be suffering from similarly rare conditions. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.14.

Consultee	Comment	Response
Wyeth	A recent report on the assessment and appraisal of oncology medicines produced by the Office of Health Economics (OHE) Consulting and the University of York[3] identified "the potential divergence between the values of patients, who directly experience the health state, and of the general public, who have been asked to make choices over hypothetical heath states which they might find difficult to fully understand. Cancer patients' preferences may be driven by specific characteristics of the disease. If someone has been told that they only have six months to live, gaining an extra two months might be worth a lot more to them than would a two-month gain if they had five years to live (over and above any discounting arising from the timing of future health effects.) As currently calculated a QALY valuation of health effects would not reflect this". The report further highlights: "From a resource allocation perspective, under the current approach all QALYs are deemed to be of equal social value. However, our literature review indicates that there is societal willingness to give priority to the worse-off (people suffering from more severe illness), even if this involves a sacrifice in aggregate health gains".	The Committee has a strong preference for expressing health gains in terms of QALYs. However, additional (non-reference case) analyses may be submitted where patients' health-related quality of life has not been adequately captured. See Guide to the Methods of technology appraisal, section 5.5.4.

[3] Assessment and appraisal of oncology medicines: does NICE's approach include all relevant elements? What can be learnt from international HTA experiences? http://www.ohe.org/lib/liDownload/634/P01%20Executive%20Summary%20V2.pdf?CFID=154093&CFTOKEN=55059206

Consultee	Comment	Response
Wyeth	Median overall survival for patients on temsirolimus is 10.9 months:  Median overall survival for patients on sunitinib is 26.4 months*:  * - *Based on the final ITT population*	Comment noted. The Committee noted that temsirolimus is a clinically effective treatment for advanced and/or metastatic renal cell carcinoma and extend overall survival. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.11. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that temsirolimus for the treatment of advanced and/or metastatic RCC would not be a cost-effective use of NHS resources. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.14.

Consultee	Comment	Response
Wyeth	Patients eligible for treatment: - Sunitinib: 1331 patients[4] in England could be treated with sunitinib (as recommended for use in FAD), - Temsirolimus: 238 patients[5] in England could be treated with temsirolimus, **if recommended**. *Pie chart provided, but not reproduced here.* Drug acquisition costs for these patients would be: - Sunitinib 15 cycles cost £62.7mln (the 1st cycle is free), equivalent to 95% of all drug costs - Temsirolimus 24 weeks treatment cost £3.4mln, equivalent to 5% of all drug costs *Pie chart provided, but not reproduced here.* If both treatments were recommended for use, giving access to a first line treatment option for all aRCC patients in the UK, 15% of the patients with poor prognosis would incur only 5% of the total drug costs.	The Committee does not consider the affordability, that is costs alone, of new technologies but rather their 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, paragraphs 6.2.6.1 – 6.2.6.3).
Wyeth	**Evidence and interpretation** In the Appraisal Consultation Document issued in February 2009, temsirolimus is described as having 'significant benefits compared with interferon- α in terms of overall survival, progression-free survival and tumour response rate' for aRCC patients with 3 of 6 prognostic factors indicating poor prognosis. Despite this recognition of the clinical effectiveness of temsirolimus, the ACD makes a negative preliminary recommendation based on the drug's cost effectiveness. The Appraisal Committee made this recommendation using the supplementary advice "Appraising life-extending, end of life treatments" issued in January 2009. The advice is an important step forward in the process of reviewing the decision rules currently adopted by NICE. However, as demonstrated by this ACD, there are still barriers that hinder patients' access to new beneficial treatments:	Comment noted. See responses below.

[4] NICE Costing template for Sunitinib (under consultation)
[5] See 'Wyeth submission to NICE", p. 51

Consultee	Comment	Response
Wyeth	- The draft supplementary advice for consultation specified that it is not intended to cover ultra-orphan drugs, but this text has been excluded from the final version. Still, the final advice is not fit for use in the appraisal of ultra-orphan drugs and Wyeth believes that as a result the Appraisal Committee was disadvantaged in its decision-making process by being led to believe that 'small groups of patients' applies to ultra-orphan drugs including temsirolimus.	The Institute have not been informed by the Department of Health that the methodology for appraising orphan conditions should differ from any other technology. See the Guide to the methods of technology appraisals.
Wyeth	- The supplementary advice is very vague in its definition of the size of the population treated, and especially in the description, or rather lack of, the decision rules to be used by the Appraisal Committee in the appraisal – in particular, what constitutes an acceptable 'additional weight' thus making a treatment 'approvable', and what the weight would be should the medicine be ultra-orphan.	The Committee considered whether drugs for ultra-orphan conditions should be appraised differently but the DH has not instructed the Institute to use different methods in appraising them. See section 4.3.14 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'. The supplementary advice does not suggest for Committee to apply a particular weight for the cost effectiveness estimate to fall within the acceptable threshold range. The Committee is asked to come to a value judgment on whether the magnitude of additional weight, that would need to be assigned to the original QALY benefits in the patient group for the cost effectiveness of the drug to fall within the current threshold range, would be acceptable in light of the evidence presented.

Consultee	Comment	Response
Wyeth	**Appraising orphan and ultra-orphan drugs** The ultra-orphan nature of temsirolimus has been recognised by both NICE and the Department of Health[6]. On the basis that the majority of Citizens Council members thought that the NHS should consider paying premium prices for drugs to treat patients with very rare diseases, the draft second edition of NICE's Social Value Judgements document, detailing principles for the development of NICE guidance, stated that "NICE has not yet been asked to assess drugs for very rare conditions or diseases (which occur in fewer than 1 in 50,000 people in the population). If NICE was asked to do so, it would have to consider its approach". Wyeth believes that temsirolimus should be appraised using a separate set of appraisal criteria for ultra-orphan drugs due to the special circumstances they present, which has previously been acknowledged both by NICE and its Citizens Council. Wyeth first raised these concerns when originally notified of NICE's intention to include Torisel in this appraisal and indicated that it would not be appropriate to appraise the drug through the Institute's existing process.	The Institute have not been informed by the Department of Health that the methodology for appraising orphan conditions should differ from any other technology. See the Guide to the methods of technology appraisals.
Wyeth	The only document issued by NICE on the appraisal of orphan and ultra-orphan drugs is available on the NICE website in its draft form that was submitted to the DoH in 2006.[7] The conclusions drawn in the document were based on the experience and the discussions NICE had had with clinicians, patients and patient groups and the Institute's Citizens' Council.	The Institute have not been informed by the Department of Health that the methodology for appraising orphan conditions should differ from any other technology. See the Guide to the methods of technology appraisals.

[6] In correspondence with Wyeth and in communications between NICE and DoH released to Wyeth under the FOI Act.

[7] Accessible from: http://www.nice.org.uk/niceMedia/pdf/smt/120705item4.pdf

Consultee	Comment	Response
Wyeth	Orphan disease was defined as one with prevalence of less than 5 per 10,000 of the population. According to that document: *"The Institute does not consider, therefore, that any changes to its processes are needed for the appraisal of conventional "orphan drugs" with a prevalence of greater than 1 in 50,000. "* In contrast, the ultra-orphan drugs have been described as follows:	Comment noted. See response above.
	"There would, however, be problems in the appraisal of drugs for very rare diseases – "ultra-orphan drugs" – largely because of their high costs. The Institute recommends that this group be defined as conditions with a UK prevalence of less that 1 in 50,000. NICE's advises the adoption of this definition for two reasons: first, it matches the prevalence criteria (less than 1000 persons in the UK) used by the National Specialist Commissioning Advisory Group in determining those conditions that should fall within its programmes; and, second, it encompasses all products that appear, both now and in the foreseeable future, to be particularly problematic."…. Treatments for ultra-orphan conditions that present special difficulties are characterised by all of the following features: *• high acquisition costs and correspondingly high ICERs;* *• use solely for an ultra-orphan disease (ie not also indicated for non-ultra-orphan diseases);* *• use in ultra-orphan diseases that are chronic, severely disabling, and/or life-threatening; and* *• potentially for life-long use;*	

Consultee	Comment	Response
Wyeth	In the same document NICE proposes that: *… separate decision rules (ie the range of ICERs considered "cost effective") will need to be developed and adopted for these products. […] based on the ICERs of those ultra-orphan drugs currently on the UK market. This will provide an implicit benchmark against which new ultra-orphan products can be evaluated. […] further work will be necessary to provide more robust data, and that a final position on cost effective ICERs will need to be confirmed through wider consultation. […] However, it appears that at current prices indicative ICERs for ultra-orphan products are in the range of £200,000 to £300,000 per QALY (ie a ten-fold increase on the decision rules currently applied in conventional appraisals).* Nevertheless, and despite this recognition, temsirolimus has still been appraised subject to NICE's standard cost-effectiveness threshold range and not surprisingly, it has failed to fall within the range of acceptability. **Furthermore, after applying the supplementary advice on "Appraising life-extending, end of life treatments", the group of aRCC patients with the poorest prognosis, the shortest life expectancy and the greatest clinical need were still denied this life-extending treatment.**	Comment noted. See response above.
Wyeth	**In conclusion** Wyeth believes that in the absence of a clear set of decision rules for the appraisal of ultra-orphan drugs, the Appraisal Committee should recommend temsirolimus for use within its ultra-orphan aRCC indication by allowing for a greater end-of-life premium due to its ultra-orphan features as described by NICE in the document cited above. This way, the difference between orphan and ultra-orphan drugs would be taken into account and the **very** small population of patients with poor prognosis aRCC would also benefit alongside the larger population with good/intermediate prognosis.	Comment noted. See detailed responses above.
Wyeth	3.1.3. The duration of bevacizumab infusion should be included to be consistent with details provided for temsirolimus in section 3.4.3. – 'The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30-minutes.'	Comment noted. This has been amended in the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.

Consultee	Comment	Response
Wyeth	4.1.15. The term low MSKCC prognostic score is open to misinterpretation and is inconsistent with the other references to prognosis. Suggest using the term 'favourable' as in section 4.1.2 for example	Comment noted. This has been amended in the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Wyeth	4.1.23. In contrast to the other technologies, there is no summary of the safety of bevacizumab despite the finding that more than twice the number of patients receiving the drug discontinued due to adverse events compared with IFN-α only (See section 4.1.6).	Comment noted. This has been clarified in the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Wyeth	4.1.24. To be consistent with section 4.1.19, this section should state that 'sorafenib was associated with significantly more adverse events…', rather than slightly.	Comment noted. This has been amended in the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Wyeth	4.2.18. Please note, as previously communicated that to NICE in our comments on the PenTAG economic model, that the current list price for Torisel 30 mg vial is £620.	Comment noted. This has been amended in the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Macmillan Cancer Support & Rarer Cancers Forum	We are extremely disappointed that the recently issued ACD on the use of bevacizaumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma is negative and we do not feel that the preliminary recommendation reflects the needs of this small patient group.	Comment noted. See detailed responses below.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	Point 4.3.2 in the ACD states "there are no second-line treatment options". Therefore the treatments considered in this appraisal provide new options for people once they have exhausted first-line treatment. The innovation that these four therapies bring to the treatment of advanced and/or metastatic renal cell carcinoma is significant and we would urge the Appraisal Committee to reconsider its decision, particularly for second-line therapies.	Comment noted. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.10, 4.3.14, 4.3.15, 4.3.18, 4.3.22, 4.3.25, 4.3.26 and 4.3.28.
Macmillan Cancer Support & Rarer Cancers Forum	It seems to us that because there have been no pharmaceutical developments in advanced and/or metastatic renal cell carcinoma since interferon came to the market, these four treatments are at a disadvantage because the comparator is old and comparatively inexpensive.	The appraisal was carried out within the context of the original scope agreed at the scoping workshop. Immunotherapy was considered the most appropriate comparator.
Macmillan Cancer Support & Rarer Cancers Forum	Point 4.3.12 notes that "temsirolimus was licensed for people with a poor prognosis and so had a very small patient population". The budget impact to the NHS of this treatment is likely to be extremely small. It is vital that NICE is able to take wider budget impact in to account in its analysis to ensure that important treatments like these are made available to those patients who would benefit from them.	The Committee consider the clinical and cost effectiveness of technologies but cannot take budget impact into account when making decisions.
Macmillan Cancer Support & Rarer Cancers Forum	In relation to point 4.3.6 of the ACD, we hope that the discussions between the manufacturer of bevacizumab and the Department of Health are concluded in time for the next Appraisal Committee meeting so that revised cost effectiveness estimates for this treatment can be considered in the analysis.	The patient access scheme for bevacizumab was confirmed by the Department of Health and incorporated into the updated analyses in time for the second appraisal Committee meeting and considered fully by the Committee. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 3.1.3.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	Point 4.3.21 states “It considered that the magnitude of additional weight that would need to be assigned to the original QALY benefits in this patient group for the cost effectiveness of the drug to fall within the current threshold range would be too great.” Please could you explain what the magnitude of additional weight would need to be to have made this acceptable within the new end-of-life guidance?	The supplementary advice does not suggest for Committee to apply a particular weight for the cost effectiveness estimate to fall within the acceptable threshold range. The Committee is asked to come to a value judgment on whether the magnitude of additional weight, that would need to be assigned to the original QALY benefits in the patient group for the cost effectiveness of the drug to fall within the current threshold range, would be acceptable in light of the evidence presented.
Macmillan Cancer Support & Rarer Cancers Forum	We are disappointed that the patient access schemes offered by the manufacturers do not reduce the cost effectiveness assumptions sufficiently to make these treatments available within the NHS. We would urge all of the manufacturers to look again and see if there is more that they can do make the cost effectiveness of these treatments acceptable to Appraisal Committee.	The Committee is not able to make recommendations on the pricing of technologies to the NHS. See Guides to the methods of technology appraisal section 6.1.8.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	We do not consider that the provisional recommendations constitute suitable guidance to be implemented by the NHS. This appraisal highlights methodological flaws in the technology appraisal process. A drug which clinicians believe is effective – when there are no other equivalent treatment options – should be recommended.	Comment noted. The Appraisal Committee has been given supplementary advice to be taken into account when appraising treatments which may be life extending. This advice addresses the notion of additional benefits not readily captured in the reference case and to have regard to the importance of supporting the development of innovative treatments that are (anticipated to be) licensed for small groups of patients who have an incurable illness. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.4. However, The Committee concluded that none of the technologies for the treatment of advanced and/or metastatic RCC would be a cost-effective use of NHS resources. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.10, 4.3.14, 4.3.15, 4.3.22, 4.3.26 and 4.3.28.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	Point 4.3.8 states "the Committee noted that bevacizumab was also licensed for a number of other indications involving much larger patient groups." We are concerned that the Appraisal Committee has interpreted the '*Appraising life-extending, end of life treatments'* guidance in this way. We believed that only the indication of the treatment being appraised would be considered in this new guidance rather than additional licence indications which a manufacturer holds for the same product. We believe that this interpretation of the additional guidance could disadvantage small groups of patients with conditions at the end-of-life and that this interpretation is not in the spirit of the additional guidance. We would therefore urge the Appraisal Committee to reconsider the bevacizumab analysis using the new guidance for end-of-life medicines.	Comment noted. The Committee considered this See section 4.3.9 of the FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma'.
Macmillan Cancer Support & Rarer Cancers Forum	We are pleased that the Appraisal Committee was able to approach this appraisal pragmatically and allow sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma to be considered separately from the rest of this appraisal.	Comment noted. No actions requested.

Consultee	Comment	Response
Macmillan Cancer Support & Rarer Cancers Forum	However, as charities dealing with patients and their families being denied treatment for kidney cancer, we are more than disappointed that the Appraisal Committee is minded to reject all of these treatments, which could make a significant impact on patients' lives, relieving symptoms and maintaining function. We believe that these treatments should be made available to those that would benefit from them, on the basis of clinical decision making, rather than on purely cost effectiveness grounds.	Comment noted. The Committee noted that the technologies are clinically effective treatments for advanced and/or metastatic renal cell carcinoma and extend overall survival. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.5, 4.3.11, 4.3.17, 4.3.19 and 4.3.24. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that the technologies for the treatment of advanced and/or metastatic RCC would not be a cost-effective use of NHS resources. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.10, 4.3.14, 4.3.15, 4.3.22 and 4.3.26 and 4.3.28.

Consultee	Comment	Response
National Kidney Federation	The National Kidney Federation welcomes the NICE recommendation on the use of Sunitinib by the NHS in a first line setting for the treatment of advanced and/or metastatic renal cell carcinoma. We must however express our disappointed that only one drug has been recommended and would make the following further comment.	Comment noted. See detailed responses below.
National Kidney Federation	In our original submission we explained that patients are individuals and it is difficult to determine the exact effect any drug will have on a given patient. It is therefore common practice to prescribe a similar type of drug should a patient have a particularly bad reaction or response to a given drug. It is essential that Consultants and Medical Teams work in partnership with the patient in determining their treatment pathway. The patients need to be advised and informed to enable them where ever possible to participate and make choices in their treatment provision. To provide this, Consultants must have the freedom to tailor a drug regime to that which best meets the needs, response and choice of an individual patient. Patients and Consultants deserve this range of therapies in order to have the ability to make that choice. In breast cancer patients for example the survival rates have increased as the range of therapies has increased.	Comments noted. For both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus (Social Value Judgments - Principles for the development of NICE guidance; principle 5).

Consultee	Comment	Response
National Kidney Federation	We are also concerned that Sunitinib is not recommended as a first line treatment for those patients with three or more of six indicators of poor prognosis. In our original sub mission we highlighted the particular difficulties of this small number (c.400) of patients. The decision seems to abandon the needs of all of these patients leaving them with no treatment options, little hope for the future and the prospect of an early death.	The Committee noted that the only current standard treatment is immunotherapy that there is an unmet clinical need. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.2. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5).
National Kidney Federation	We can only assess the evidence presented to us by NICE on the drugs they selected for appraisal. It would therefore seem from a lay perspective that the drug Temsirolimus is a clinically acceptable solution for this small group of patients; *'The Committee was persuaded that Temsirolimus is a clinically effective first-line treatment for people with a poor prognosis'.* *'The Committee noted that Temsirolimus demonstrated a statistically significant gain in terms of overall survival, progression-free survival and tumour response rate compared with IFN-á'* It is obvious from the original ACD that the cost effectiveness against the conventional NICE threshold was a problem. It would also appear that the current end of life care supplementary guidance and the low patient numbers still puts cost effective treatment for these patients beyond the NICE threshold?	The Committee consider the clinical and cost effectiveness of technologies but cannot take budget impact into account when making decisions.

Consultee	Comment	Response
National Kidney Federation	Following the Prof Mike Richards report and the action taken by the Secretary of State for Health we had high hopes that the situation would change particularly with relation to the assessment of orphan drugs (see our previous comments) The NKF feels strongly this is the area where patient low numbers and costs are critical. In reality since not all of this group of patients would be suitable for treatment, the numbers would be less than 400 and the actual overall cost of treatment to extend their lives miniscule in it effect on NHS budgets.	The Institute have not been informed by the Department of Health that the methodology for appraising orphan conditions should differ from any other technology. See the Guide to the methods of technology appraisals.
Royal College of Nurses	The Royal College of Nursing welcomes the opportunity to review the Appraisal Consultation Document (ACD) on the use of bevacizumab, sorafenib, sunitinib (second-line) and temsirolimus for the treatment of advanced and/or metastatic renal cell carcinoma. *Nurses working in this area of health have reviewed the ACD and have nothing to add to this appraisal document.*	Comment noted. No actions requested.
Royal College of Nurses	*The RCN would welcome guidance to the NHS on the use of these drugs for the treatment of advanced and/or metastatic renal cell carcinoma.*	Comment noted. No actions requested.
Expert 1	My comments on the evaluation report of 03/02/09 is as follows, (1) I congratulate the committee on being the first adopter of the new end-of-life drugs criteria.	Comment noted. No actions requested.

Consultee	Comment	Response
Expert 1	(2) Sorafenib should be allowed for second line treatment after interferon. The UK still has a significant cohort of such patients who have only ever been treated with interferon and who deserve treatment with a TKI. This cohort will also rapidly dwindle in number so will not be a recurrent cost in the future. Sorafenib has the best evidence but would be denied under the current guidance. I have seen emails stating that sunitinib will be allowed for patients who have received interferon although I have not seen formal clarification of this and goes against the best available randomised trial evidence which would be for sorafenib.	Comments noted. Sunitinib can be considered as a treatment option for those people with advanced and/or metastatic RCC who are currently receiving immunotherapy or who have had immunotherapy before the release of final recommendations to ensure that they are not disadvantaged by the guidance. The Committee concluded that sorafenib for the second-line treatment of advanced and/or metastatic RCC for people in whom immunotherapy had failed would not be a cost-effective use of NHS resources. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.22.

Consultee	Comment	Response
Expert 1	(3) There will be a small cohort of patients who are truly intolerant of sunitinib, and therefore are likely to be intolerant of sorafenib as well because these belong to the same category of drug, and for these patients there should be the recommendation to use either bevacizumab/interferon or temsirolimus instead as clinically appropriate.	Comment noted. The Committee noted that there is an unmet clinical need. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.2. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5).
Expert 2	I attach a meta analysis: (http://www.docguide.com/news/content.nsf/PaperFrameSet?OpenForm&newsid=852571020057CCF68525754E002DC1AD&topabstract=1&u=http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Abstract&list_uids=19173737) of current RCC treatments which I would like to draw to the attention of the NICE team. For a patient representative this analysis presents a compelling case for the clinical efficacy of all the drugs under review but also raises key questions	Comment noted. The Committee considered all the evidence submitted, including evidence from clinical trials, patient and clinical experts, the Assessment Group's economic analysis and the manufacturers' submissions. It also carefully considered the comments received from consultees and commentators in response to the Assessment Report. The Assessment relies on the available evidence submitted to the Institute and that retrieved from the published literature by the assessment group.

Consultee	Comment	Response
Expert 2	1. Sunitinib is rated as the most clinically effective treatment but all of the drugs are deemed to be clinically effective . The availability of Temsirolimus to those patients with poor prognosis is deemed to be very important	Comment noted. The Committee noted that there is an unmet clinical need. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' section 4.3.2. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5).
Expert 2	2. Current NICE guidance has led to some confusion about first and second line treatments in relation to previous treatments by interferon -Alpha and clinical trials . We need a clear statement of the circumstances when the prescribing of Sunitinib will be recommended	Comments noted. Sunitinib can be considered as a treatment option for those people with advanced and/or metastatic RCC who are currently receiving immunotherapy or who have had immunotherapy before the release of final recommendations to ensure that they are not disadvantaged by the guidance.
Expert 2	3. It would seem perverse to only allow one drug --Sunitinb -- for RCC patients . The other drugs should be at the discretion of the prescibing clinician matching the individual characteristics of that patient . One size does not fit all and clinicians should not have only 1 bullet in their gun.	Comment noted. For both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5).

Consultee	Comment	Response
Expert 2	4. The NICE guidance does not allow for the probability that combination therapies of these drugs are the gold standard treatments of the very near future. The NICE team need to consider their response to this obvious opportunity	Comment noted. The appraisal was carried out within the context of the original scope agreed at the scoping workshop.

Consultee	Comment	Response
Expert 2	5 The analysis references the concern of the authors that the NICE cost benefit analysis is so dominant in the debate about drug availability that cost concerns drastically limit patient access to the best and most modern treatments	Comment noted. The Committee noted that the technologies are clinically effective treatments for advanced and/or metastatic renal cell carcinoma and extend overall survival. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.5, 4.3.11, 4.3.17, 4.3.19 and 4.3.24. However, for both legal and bioethical reasons the Committee must take account economic considerations and cost effectiveness of the technologies (Social Value Judgments - Principles for the development of NICE guidance; principle 5). The Committee concluded that the technologies for the treatment of advanced and/or metastatic RCC would not be a cost-effective use of NHS resources. See FAD 'bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma' sections 4.3.10, 4.3.14, 4.3.15, 4.3.22 and 4.3.26 and 4.3.28.

Comments received from commentators

Commentator	Comment	Response
NHS Quality Improvement Scotland	Whether you consider that all the relevant evidence has been taken into account. **Yes**	Comment noted. No actions requested.
NHS Quality Improvement Scotland	Whether you consider that the summaries of clinical and cost effectiveness are reasonable interpretations of the evidence. **Yes**	Comment noted. No actions requested.
NHS Quality Improvement Scotland	Whether you consider that the provisional recommendations of the Appraisal Committee are sound and constitute a suitable basis for the preparation of guidance to the NHS. **No-there are currently a significant number of kidney cancer patients receiving interferon therapy as this is the only active treatment available,these patients should be allowed to switch to sunitinib if they develop progression**	Comments noted. Sunitinib can be considered as a treatment option for those people with advanced and/or metastatic RCC who are currently receiving immunotherapy or who have had immunotherapy before the release of final recommendations to ensure that they are not disadvantaged by the guidance.