NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

The following documents are made available to the consultees and commentators:

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

2. **Consultee and commentator comments on the Appraisal Consultation Document** from:
   - Ipsen
   - Kidney Cancer Support Network
   - Kidney Cancer UK
   - Kidney Research UK
   - NHS England
   - National Cancer Research Institute

   The Department of Health and Pfizer had no comments

3. **Comments on the Appraisal Consultation Document from experts:**
   - Robert Hawkins, Professor – Clinical Expert, nominated by Ipsen

4. **Comments on the Appraisal Consultation Document received through the NICE website**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal

Cabozantinib for previously treated advanced renal cell carcinoma

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

Definitions:

Consultees – Organisations that accept an invitation to participate in the appraisal including the companies, national professional organisations, national patient organisations, the Department of Health and the Welsh Government and relevant NHS organisations in England. Consultees can make a submission and participate in the consultation on the appraisal consultation document (ACD; if produced). All non-company consultees can nominate clinical experts and/or patient experts to verbally present their personal views to the Appraisal Committee. Company consultees can also nominate clinical experts. Representatives from NHS England and clinical commissioning groups invited to participate in the appraisal may also attend the Appraisal Committee as NHS commissioning experts. All consultees have the opportunity to consider an appeal against the final recommendations, or report any factual errors, within the final appraisal determination (FAD).

Clinical and patient experts and NHS commissioning experts – The Chair of the Appraisal Committee and the NICE project team select clinical experts and patient experts from nominations by consultees and commentators. They attend the Appraisal Committee meeting as individuals to answer questions to help clarify issues about the submitted evidence and to provide their views and experiences of the technology and/or condition. Before they attend the meeting, all experts must either submit a written statement (using a template) or indicate they agree with the submission made by their nominating organisation..

Commentators – Commentators can participate in the consultation on the ACD (if produced), but NICE does not ask them to make any submission for the appraisal. Non-company commentator organisations can nominate clinical experts and patient experts to verbally present their personal views to the Appraisal Committee. Commentator organisations representing relevant comparator technology companies can also nominate clinical experts. These organisations receive the FAD and have opportunity to report any factual errors. These organisations include comparator technology companies, Healthcare Improvement Scotland any relevant National Collaborating Centre (a group commissioned by NICE to develop clinical guidelines), other related research groups where appropriate (for example, the Medical Research Council and National Cancer Research Institute); other groups such as the NHS Confederation, the NHS Commercial Medicines Unit, the Scottish Medicines Consortium, the Medicines and Healthcare Products Regulatory Agency, the Department of Health, Social Services and Public Safety for Northern Ireland).

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 NICE reserves the right to summarise and edit comments received during consultations, or not to publish them at all, where in the reasonable opinion of NICE, the comments are voluminous, publication would be unlawful or publication would be otherwise inappropriate.

Confidential until publication

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comments received from consultees

Nominating organisation	Comment [sic]	Response
Ipsen	**<u>Section 1: Everolimus as a comparator</u>** ACD Section 4.4 "[…]. *Given the recent changes in the recommendations for everolimus, and the clinicians' preference to use everolimus later in treatment, the committee appreciated that everolimus might be used after 1, but also after 2 or 3 previous treatments. The committee would welcome comments on the likely positioning of everolimus in the treatment pathway, following recent NICE guidance. The committee concluded that everolimus was a relevant option after 1 or 2 previous treatments alongside axitinib and nivolumab*." In response to the committee's invitation for comments on the likely positioning of everolimus we have sought clinician feedback to understand whether everolimus is now being used in the treatment pathway for the second (2nd) and/or third (3rd) line treatment of aRCC. Twenty clinicians were approached for detailed discussions with 15 responses received. Of these none positioned everolimus in the 2nd line setting, instead preferring either nivolumab or axitinib. Only one of the 15 clinicians stated that everolimus could considered as a possible option 3rd line, with the remaining 14 stating they use either axitinib or nivolumab 3rd line. Those 14 view everolimus as a fourth (4th) line option. While we accept that the health system in Scotland is not directly related to that in England and Wales it may be useful for the Committee to consider the uptake of everolimus since it received SMC approval in November 2014, bearing in mind that axitinib has been funded in Scotland since November 2013. Significant usage would be reflected in the choice of everolimus as an appropriate comparator and current standard of care in SMC appraisals and this is not the case. In the recent SMC appraisal of nivolumab for the treatment of aRCC[2], clinical experts advised SMC that axitinib was the key comparator based on use in clinical practice. In addition, at the SMC's committee meeting held in public on 2nd May 2017, at which both cabozantinib and nivolumab (as a resubmission) for the treatment of aRCC were discussed, it was noted that axitinib was the appropriate comparator.	Thank you for your comment. Given the clinicians' preference to use everolimus later in treatment, the committee appreciated that use of everolimus after the Cancer Drugs Fund reconsideration guidance on everolimus was likely to shift down the treatment pathway. See sections 4.3 and 4.4 of the Final Appraisal Determination (FAD) for further details.

Nominating organisation	Comment [sic]	Response
	In addition to the clear position from the clinical community that everolimus is not used in the 2nd line setting, and only used 3rd line in only rare/exceptional circumstances, there are a further three important points which should also be considered: 1. The information submitted by NHS England during the re-appraisal of everolimus in aRCC (TA432) which stated[3]: "*16. NHS England now notes that the treatment pathway for patients with advanced and previously TKI-treated renal cancer may become more complicated with the potential inclusion of nivolumab for the TKI 1-prior and 2-prior populations, this being dependent on the currently running NICE appraisal. NHSE notes that the main evidence base for the benefit of nivolumab in renal cancer lies in a trial which compared nivolumab with everolimus. NHSE considers that any NICE recommendation for nivolumab within its licensed indication is likely to result in considerable use of nivolumab either as 2nd line treatment with axitinib being used 3rd line (as there is as yet no biological reason shown why axitinib should not work as well post-nivolumab as pre-nivolumab) or nivolumab used as 3rd line post-axitinib. Either of these scenarios would displace any potential availability of everolimus to 4th line therapy.* *17. NHS England notes that the relevance and importance of everolimus in the treatment of renal cancer has reduced, noting that the clinical expert input into the nivolumab appraisal clearly stated that there was clinical preference for the use of axitinib 2nd line rather than everolimus 2nd line. At present, the potential position of everolimus would be as 3rd line in the treatment pathway. This assessment may further change if nivolumab is recommended by NICE within its licensed indication and in which case everolimus would be positioned as a potential 4th line of treatment*." This is entirely in line with the feedback Ipsen has received from clinicians regarding the place of everolimus in the treatment pathway. Since nivolumab for the treatment of aRCC has now received positive NICE guidance (TA417)[4] it appears that everolimus is generally viewed as a 4th line treatment, regardless of the availability of cabozantinib. 2. In the event the provisional recommendation for cabozantinib stands, it will endorse the illogical position whereby two drugs (axitinib and nivolumab), which are confirmed by the ACD to be less cost-effective than cabozantinib, will be available for use while the more cost-effective drug (cabozantinib) will be rejected simply because it is not cost-effective against a drug (everolimus) that is not used in clinical practice in these lines of therapy. We understand that this is the product of sequential single technology appraisals in the same therapy area, but it is nonetheless quite clearly a perverse outcome.	The FAD recommends cabozantinib within its marketing authorisation for advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF) targeted therapy.

Nominating organisation	Comment [sic]	Response
	3. The decision to not recommend cabozantinib on the basis that is not cost-effective versus everolimus fails to take into account the fact that this appraisal is considering *two* distinct lines of treatment. If everolimus were accepted as the appropriate comparator in the 2nd line setting, it cannot at the same time also be the comparator in the 3rd line setting. That is, once everolimus is used in second line, the comparator for third line must be either nivolumab or axitinib. Similarly, if everolimus is considered to be the appropriate comparator in third line, then the treatments which precede it would have to be nivolumab or axitinib. In either case, cabozantinib becomes the most cost-effective option in whichever position is occupied by axitinib or nivolumab.	
Ipsen	**Section 2: Utilities** We appreciate that both the Committee and ERG had concerns about the utility values from the METEOR trial, citing general population utility estimates from Ara et al. 2010.[5] In considering the validity of the METEOR utility estimates, we note the statement in the first ACD (section 4.20) and second ACD (section 4.22) which acknowledged the potential impact of using the EQ-5D-5L[6] in METEOR. We would like to reiterate the findings of the Devlin et al. 2016 publication[6], which suggest that higher values with ED-5D-5L may be expected compared with EQ-5D-3L. This may at least partly explain the differences observed between estimates from METEOR and the age-specific general population utility values. Both ACDs also state a preference for trial-based values which, in fact, is the case with the METEOR values. To substitute these for values from the AXIS trial introduces other potential complications, already acknowledged by the Committee and ERG. Indeed, we were requested to remove AXIS as a source of efficacy data in the network meta-analysis. We would have liked to understand the effect of prior cytokine use on patients' health, since in the axitinib appraisal (TA333)[7] separate values were provided for prior-cytokine and prior-VEGFR patients. Unfortunately, these values are redacted in the NICE documents and we have not been able to find them in any other publication. If utility estimates for the prior cytokine group differ from the utility estimates for the prior VEGFR-group, the proposed AXIS utility values which aggregate these two groups may not be appropriate. Nonetheless, acknowledging the concerns regarding METEOR values, we have investigated which other utility values have most recently been used and accepted in appraisals in aRCC. These are detailed in Table 1.	Thank you for your comment. The committee generally preferred sourcing utility and effectiveness from the same trial. However, it agreed that some of the utility values from METEOR appeared high, particularly the utility value before disease progression. The committee concluded that it would take into account utility values from both METEOR and AXIS in its

<table>
<tr><th>Nominating organisation</th><th>Comment [sic]</th><th>Response</th></tr>
<tr><td></td><td>Table 1: Utility values for stable and progressed patients with aRCC
<table>
<tr><th></th><th>Value</th><th>Source</th><th>Use in NICE appraisals</th></tr>
<tr><td>Base case</td><td>PFS – 0.817
PD – 0.777</td><td>METEOR</td><td></td></tr>
<tr><td>CheckMate Scenario</td><td>PFS – 0.76
PD – 0.70</td><td>CheckMate025, everolimus arm</td><td>Used in TA417[4] (published Nov 2016)</td></tr>
<tr><td>Sorafenib scenario</td><td>PFS – 0.76
PD – 0.68</td><td>Sorafenib utility for second line[8]</td><td>Used in TA432[3](published Feb 2017)</td></tr>
<tr><td>AXIS scenario</td><td>PFS – 0.69
PD – 0.61</td><td>AXIS</td><td>Used in TA333[7] (published in Feb 2015)</td></tr>
</table>
Key: PFS = Progression-Free Survival; PD = Progressed Disease.
In the event that other non-METEOR utility values are preferred by the Committee, we consider that the more plausible source for a set of alternative utilities is the everolimus arm of the CHECKMATE trial. That is, a utility value for PFS of 0.76 and for PD of 0.70. The CHECKMATE trial is more in line with the METEOR trial both in its baseline population and to the extent that it reflects current practice in both prior and subsequent lines of treatment.</td><td>decision-making. The committee noted that using either set of utility values would not impact the cost-effectiveness conclusions to a degree where the committee would change its recommendations. See sections 4.20 and 4.26 of the FAD for further details.</td></tr>
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Comments received from clinical experts and patient experts

Nominating organisation	Comment [sic]	Response
Clinical expert	Whilst I cannot comment of the technical assessment of cost effectiveness I will make a number of observations from a clinical perspective. 1. From a practical point of view the main comparators for cost effectiveness is really Axitinib or Nivolumab. In the vast majority of patients Everolimus will be used as a third / fourth line therapy after failure of Cabozantinib/Nivolumab/Axitinib. 2. Given the above the key economic comparator is not Everolimus but Axitinib and/or Nivolumab. 3. In reality most patients will be considered for 2 TKIs (first line therapy and one other) and Nivolumab – the order of second TKI and Nivolumab will vary according to various clinical factors but certainly, I would consider the benefits of three lines of TKI (Sunitinib/Pazopanib,	Thank you for your comment. Given the clinicians' preference to use everolimus later in treatment, the committee

Nominating organisation	Comment [sic]	Response
	Cabozantinib and Axitinib) are likely to be less than 2 lines and Nivolumab. It would therefore be reasonable to restrict clinical choice to 2-lines of TKI rather then the potential to have 3-lines. 4. Although I do not have access to the commercial discount figures I imagine Everolimus has been approved as a result of a substantial discount that happened after the approval of Nivolumab. It seems that Cabozantinib is now being compared with reduced price of Everolimus whereas Nivolumab was compared with the full price – this potentially leads to the rejection of Cabozantinib and the acceptance of Nivolumab – this seems illogical since as I understand it, the NICE appraisal suggests Cabozantinib is more cost effective than Nivolumab?	appreciated that use of everolimus after the Cancer Drugs Fund reconsideration guidance on everolimus was likely to shift down the treatment pathway. Therefore, the relevant comparators were axitinib and nivolumab. See sections 4.3 and 4.4 of the FAD for further details.
NHS England	**<u>NHS England comment re place of everolimus in the treatment of advanced/metastatic renal adenocarcinoma</u>** 1. The two established treatment options as 1st line systemic therapy are the multi-targeted tyrosine kinase inhibitors, sunitinib and pazopanib (both include VEGF inhibition). These are either/or options as 1st line treatment. 2. Axitinib is NICE-approved after 1st line treatment. 3. Nivolumab is NICE-approved as either 2nd or 3rd line treatment. 4. Everolimus is now NICE-approved, its license being after VEGF-targeted treatment. 5. NHS England is shortly to consult on a treatment algorithm which sets out the following (active consideration of best supportive care occurs with each therapy): - 1st line: sunitinib or pazopanib	Thank you for your comment. Given the clinicians' preference to use everolimus later in treatment, the committee appreciated that use of

Nominating organisation	Comment [sic]	Response
	- 2nd line: axitinib or nivolumab or everolimus - 3rd line: axitinib or nivolumab or everolimus depending on what was used before as 2nd line treatment - 4th line: axitinib or nivolumab or everolimus depending on what was used as 2nd and 3rd line treatment. 6. Since all the 2nd/3rd/4th line treatment options have differing modes of action, there is biological plausibility in for example everolimus being active after nivolumab or axitinib. This biological plausibility justifies the sequential set of treatment options in the algorithm as stated above. 7. Just because the algorithm states 4 potential lines of treatment does not mean that NHS England expects all patients to proceed from 1st line to 4th line. Only a minority of patients will be fit enough and motivated enough to explore all 4 options. 8. Clinicians inform NHS England that everolimus is used less than the other options of axitinib and nivolumab. 9. Cabozantinib is a multi-targeted TKI, sharing some common targets as the other TKIs but also has some novel targets. There is biological plausibility that it would show activity in patients treated with other TKIs and its main registration trial included patients previously treated with VEGF-targeted treatments and the programmed death 1 receptor or its ligands. 10. If NICE recommends the use of cabozantinib (this being an optimised recommendation), NHS England would see it as being an additional options as 2nd/3rd/4th/and even 5th line treatment. NHS England recognises that the number of patients diminishes significantly with each line of therapy on account of both disease-orientated reasons and patient choice and also understands that one patient may tolerate one TKI better than another.	everolimus after the Cancer Drugs Fund reconsideration guidance on everolimus was likely to shift down the treatment pathway. See sections 4.3 and 4.4 of the FAD for further details.
Kidney Cancer Support Network	In a second Appraisal Consultation Document (April 2017), the NICE technology appraisal committee have again not recommended cabozantinib for use within its marketing authorisation for the treatment of advanced renal cell carcinoma (RCC) in adults after vascular endothelial growth factor (VEGF)-targeted therapy. This is despite cabozantinib's proven effectiveness at prolonging the life of kidney cancer patients by 4.9 months compared to everolimus in the METEOR trial, and impressive progression-free survival benefit in patients with spread to their bones, reducing the risk of death by 46% compared with everolimus in patients with bone metastases. In addition, cabozantinib has demonstrated clinically significant benefit over everolimus in all three clinical trial efficacy endpoints,	Thank you for your comment. The FAD recommends cabozantinib within its marketing

Nominating organisation	Comment [sic]	Response
	namely progression-free survival, overall survival and response rate. This finding is unprecedented in recent clinical trials with RCC agents. The Kidney Cancer Support Network's response to the second cabozantinib ACD has been informed by the views of advanced kidney cancer patients who are taking cabozantinib as part of a clinical trial or through a Managed Access Programme in the UK.	authorisation for advanced renal cell carcinoma in adults after VEGF-targeted therapy.
Kidney Cancer Support Network	**1. Treatment options in the second- and third-line settings** Cabozantinib was compared to everolimus in the METEOR trial, and was proven to be a clinically effective and well-tolerated drug, leading to its designation as a **'promising innovative medicine' for advanced RCC by the Medicines and Healthcare products Regulatory Agency (MHRA)** last year. Cabozantinib is positioned as a second-line treatment for advanced RCC after VEGF-targeted therapy. The ACD recognises that cabozantinib is more effective than everolimus, and probably more effective than axitinib (the two drugs have not been compared directly in a randomised controlled clinical trial), although it is associated with more adverse events. The ACD states, "….despite new treatments recently being recommended by NICE, there remained limited treatment options and an unmet clinical need for some people with advanced renal cell carcinoma." The ACD mentions the three treatment options available to advanced RCC patients in the second- or third-line setting as recommended by NICE guidance, namely nivolumab, everolimus and axitinib. However, it seems that in clinical practice, usually nivolumab or axitinib are given in the second-line setting, and if patients fail second line treatment they progress on to the alternative drug (either nivolumab or axitinib). Everolimus appears to be reserved for fourth-line treatment when all other options have failed. This situation is confirmed by the fact that, although everolimus is now available for routine clinical use in NHS England in the second-line setting or later, we could only find 2 patients who are currently taking the drug from our Kidney Cancer Support Network community of over 1,000 kidney cancer patients. This is anecdotal evidence that, although everolimus is now recommended after 1 or more lines of VEGF-targeted therapy (which includes TKIs), everolimus does not appear to be a "relevant option after 1 or 2 previous treatments alongside axitinib and nivolumab" as stated in the ACD, and is not being used in routine clinical practice on a regular basis. This provides real world evidence on the positioning of everolimus in the treatment pathway for advanced RCC in the fourth-line setting after failure of nivolumab and axitinib. Further to the recent NICE guidance following the Cancer Drugs Fund reconsideration of everolimus, the ACD concludes that "everolimus is a relevant option after 1 or 2 previous treatments alongside	Thank you for your comment. Given the clinicians' preference to use everolimus later in treatment, the committee appreciated that use of everolimus after the Cancer Drugs Fund reconsideration guidance on everolimus was likely to shift down the treatment pathway. See sections 4.3 and 4.4 of the FAD for further details.

Nominating organisation	Comment [sic]	Response
	axitinib and nivolumab". However, we would question this statement and suggest patients seek a second opinion if they are prescribed everolimus in the second-line setting (unless nivolumab is contra-indicated due to an autoimmune condition), particularly when nivolumab has been proven to be more effective and better tolerated: *"I was on pazopanib …… when my oncologist determined that it was starting to fail. At that point I was advised that everolimus was to be made available to me …….. Initially side effects were minimal, however about a month [sic] I started to get very bad mouth ulcers, which took a few weeks to clear up, fatigue and tiredness. Also experienced anaemia and had 2 blood transfusions. I suffered from nosebleeds, mainly when blowing my nose! Lung condition didn't help and was experiencing dry cough and breathlessness as well. Experienced lots of indigestion also had mild doses of feeling shaky and shivery. Ct scan showed that everolimus was struggling and the decision to try for Nivolumab taken in Feb/March 2016……This new drug has enabled me to lead as normal a life as possible; side effects have been minimal although I have lost some weight (around 6lbs). I do have some itchiness on lower legs and arms but this is dealt with by taking standard over the counter antihistamines. I am finding Nivolumab kinder on my system than Everolimus previously."* We appreciate the cost per QALY considerations implicit in these decisions; however, clinicians should have the ability to choose the most effective treatments for individual patients from those available, and **without cabozantinib, the clinician's choice of treatment is seriously compromised**. Without treatment alternatives in the second-line setting and later, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life: *"Whilst I have not had direct experience of taking Cabozantinib as I am still responding to Pazopanib, I have read both the clinical trial reports and real world patient experience. I believe that this would form a useful addition to the portfolio of drugs available to clinicians and will be especially useful for those patients with bone metastasis. The addition of more potential drugs would introduce more competitive pricing between suppliers."* Current second- and third-line treatment options are not effective for everyone, and can be difficult to access. Undue restrictions in accessing cabozantinib would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the second-line setting and beyond would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient. Cabozantinib will also address the massive unmet need for treatment options in the third-	The FAD recommends cabozantinib within its marketing authorisation for advanced renal cell carcinoma in adults after VEGF-targeted therapy.

Nominating organisation	Comment [sic]	Response
	line setting and later. The following statements are from a patient carer and two patients talking about the importance of having choice of treatment in the second- and third-line setting: *"I have used sutent, pazopanib and now axitinib for almost five years. When Axitinib is done, I want to be able to turn to Cabozantinib as I have a bone met. Please give me the choice."* *"In response to cazantinib* [sic] *not being approved by NICE, this is a drug that had been mentioned to me as a next step to help keep my kidney cancer at bay, it could give me valuable extra time with my two young daughters aged 4 & 2 years old. Without this medication my girls could lose their mummy too soon & they don't deserve that. This could help so many people live longer; everybody is worthy of that chance. Please think again."*	
Kidney Cancer Support Network	**3. Cost effectiveness** We are disappointed that **yet again another drug for advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups (a rare cancer):** Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying these patients access to life prolonging treatments during a desperately difficult time for both themselves and their families. We understand that cabozantinib is expensive, and we appreciate the budgetary implications, but nonetheless NICE and the manufacturers must negotiate and find a way to make this new and innovative drug available to the patients who need it; failure to do so would be seen as failure of professional competence. NICE and the manufacturer need to think outside the box to agree an alternative funding process, and work collaboratively to negotiate an acceptable patient access scheme to ensure kidney cancer patients who need it can have access to this latest clinically effective drug. *"My dad's consultant has suggested that should nivolumab stop working then this would be the next step. He specifically mentioned that Cabozantinib was more effective on bone mets than other lines of treatment, which we took as a positive since dad has mets on his spine. If this wasn't an option I think we'd be at the end of the line as dad has had IL2, sutent and axitinib prior to nivolumab. It really would be a matter of life and death and to know that there is something there that could extend life but wasn't available would be heart breaking. I know there has to be assessments around cost versus impact, but given dad's history it might have been felt that nivolumab wouldn't work when it has - he's been on it for almost a year now. Some weren't as lucky as dad and missed nivolumab. I'd hate to see this happen again."*	Thank you for your comment. The FAD recommends cabozantinib within its marketing authorisation for advanced renal cell carcinoma in adults after VEGF-targeted therapy.

Nominating organisation	Comment [sic]	Response
Kidney Cancer UK	Kidney Cancer UK is very disappointed to hear that at the midpoint of the Single Technology Appraisal (STA) of cabozantinib, NICE is considering NOT recommending its use within the NHS. Having a variety of targeted therapy options is vital for patients with advanced kidney cancer; providing hope and extra months and years of life. Different patients respond positively to different medicines. Providing a variety of therapeutic options should also help patients find a medicine that works for them. Adding cabozantinib to the second, third, fourth-line treatment options and beyond provides an option that could work really well for some patients; making kidney cancer a chronic disease rather than fatal. An example of cabozantinib working well, is described by David Chessum, who shared his experience with us on a video for supporters of Kidney Cancer UK. Please view his video for more details. https://www.youtube.com/watch?v=9asTUb1CZRU His experience of cabozantinib has been very positive: his quality of life has improved and he no longer has to deal with severe diarrhoea, a side-effect of his previous drug regime. Cabozantinib has given him a much better quality of life, something we hope will be strongly considered during the NICE appraisal.	Thank you for your comment. The FAD recommends cabozantinib within its marketing authorisation for advanced renal cell carcinoma in adults after VEGF-targeted therapy.
Kidney Cancer UK	One issue that has arisen from the recently released Appraisal Consultation Document (ACD) is the lack of guidance and standardisation for doctors regarding the sequence of second-line treatments onwards. Currently axitinib, nivolumab and everolimus are recommended by NICE as second-line treatments. Sunitinib and pazopanib are recommended as first-line treatments. In reality, the treatments given as a second-line treatment and beyond are very varied: the recommended first-line drugs are often given as fifth-line drugs and some second-line drugs are rarely prescribed at all. The 2016 Kidney Cancer UK annual survey requested information about which drugs had been taken by each responder. 111 people took the survey, 34 had taken medicine for advanced kidney cancer. • The first-line drugs were split fairly evenly between pazopanib and sunitinib, 1 person each took interleukin, everolimus (trial) and sorafenib (trial). • 13 people went on to take a second-line drug; 7 took axitinib, 5 took either the other first-line drug (pazopanib or sunitinib), one advanced to interleukin 2. • 7 people advanced to a third-line drug, 5 of which took nivolumab, 1 pazopanib and 1 axitinib. • 1 person had taken a fourth-line drug, which was sunitinib (a first-line drug). • 1 person advanced to a fifth-line drug (axitinib). The data from our survey indicated that everolimus was not taken once as a second-line or beyond drug. Only once was it taken as a first-line treatment during part of a clinical trial. Everolimus is the drug that cabozantinib has been compared to in the METEOR clinical trial so its use is of relevance in	Thank you for your comment. Given the clinicians' preference to use everolimus later in treatment, the committee appreciated that use of everolimus after the Cancer Drugs Fund reconsideration guidance on everolimus

Nominating organisation	Comment [sic]	Response
	the STA. Everolimus was previously available on the old Cancer Drug Fund and Kidney Cancer UK is pleased that everolimus (an mTOR inhibitor) has recently been recommended by NICE through its rapid appraisal scheme. Everolimus is important as it offers an alternative way of attacking kidney cancer tumour cells compared to TKI's or immunotherapy, but we would like to ask why it is not being recommended by doctors for use on the NHS.	was likely to shift down the treatment pathway. See sections 4.3 and 4.4 of the FAD for further details.
Kidney Cancer UK	We certainly would welcome more research and guidelines in the area of the sequencing of second-line treatments and beyond. We understand that many doctors use the EAU (European association of urology) guidelines but there are no firm conclusions on the sequencing of drugs beyond second-line treatments. "No firm recommendations can currently be made as to the best sequence of targeted therapy, beyond the recommendation that VEFG-targeted therapy should be used for patients with good- and intermediate-risk disease."[1]. We feel this issue should be addressed in the near future and perhaps a UK-based set of guidelines should be established, due to the variations in NICE recommendations compared to Europe drug licencing. We sincerely hope that cabozantinib is recommended by NICE in England and Wales: the wider the choice of available drugs the better potential outcomes for patients with advanced kidney cancer. Cabozantinib has been shown to provide a tolerable range of side-effects that can benefit some patients quality of life. This is invaluable. We also envisage an era of medicine where combinations of different targeted therapies are utilised and specific medicines are given to people with appropriate genetic profiles, to produce even better survival rates; we feel that cabozantinib could be very useful in this approach. We hope that the area of multiple second-line therapies continues to evolve and expand within the UK, as it is in other countries across the world.	Thank you for your comment. The FAD recommends cabozantinib within its marketing authorisation for advanced renal cell carcinoma in adults after VEGF-targeted therapy.
Kidney Research UK	NICE has stated Cabozantinib is **not** recommend by NICE within its marketing authorisation for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF) targeted therapy, but has acknowledged that Cabozantinib improved progression-free survival compared to everolimus. However, (Section 4.30) NICE acknowledges that Cabozantinib is an innovative treatment. Clinical experts stated that because of the product's multi-targeted approach, Cabozantinib would likely have additional benefits for some patients. They also stated that the product would be highly valued in patients whose disease is resistant to standard tyrosine kinase inhibitors (TKIs) and may not have responded to Nivolumab and that Cabozantinib could fulfil an unmet need in this group of patients. **Kidney Research UK support this statement as clinicians are best placed**	Thank you for your comment. The FAD recommends cabozantinib within its marketing authorisation

Nominating organisation	Comment [sic]	Response
	to fulfil the clinical needs of patients and this offers patients improved progression-free survival compared to those treated with standard therapy . **Current Practice** The committee stated they were aware there remained limited treatment options and an unmet need for people with advanced renal cell carcinoma. Especially those patients whose disease is resistant to standard TKIs and have not responded to Nivolumab .**We support this statement as treatment options are limited and patients have the right to be given a choice of a treatment that is more effective than everolimus and axitinib and are willing to accept more adverse events** **Clinically relevant sub groups of patients** The committee accepted that it would consider Cabozantinib for a patient population where people had had one or two previous treatments as a whole. **We fully support this statement.** **Section 5.1** The Department of Health and Ipsen have stated that Cabozantinib will be made available to the NHS within the parameters of a confidential patient access scheme (PAS) which makes Cabozantinib available with a discount. **We are heartened to see that the product will be available for a sub group of patients and would like to see if being made available for all patients who would derive most benefit.**	for advanced renal cell carcinoma in adults after VEGF-targeted therapy.

Comments received from commentators

Nominating organisation	Comment [sic]	Response
Queen Mary university of London	I'm writing on behalf of the National Renal cancer clinical studies group. We were disappointed that cabozantinib was rejected. The most recent European guidelines (Powles et al) state that both cabozantinib and nivolumab have superseded other drugs, such as axitinib and everolimus in this space. Therefore from a clinical perspective, cabozantinib should be used preferentially over axitinib and everolimus. Axitinib and everolimus can be considered to have similar efficacy, with no clear survival benefit, which is not the case for cabozantinib or nivolumab. The renal cancer space has become complex due to the sequential availability of drug and NICE making prospective but not retrospective assessment of agents.	Thank you for your comment. The FAD recommends cabozantinib within its marketing

Nominating organisation	Comment [sic]	Response
	The CSG respects the NICE process, and welcome cost-assessment exercises to ensure all aspects of healthcare are treated with parity. Nevertheless, cabozantinib is one of only 2 agents to show clear survival benefit in renal cancer, and therefore it should be potentially prioritised over other agents. I hope this is helpful and would be very happy to discuss or clarify over the telephone or in person.	authorisation for advanced renal cell carcinoma in adults after VEGF-targeted therapy.

The following consultees/commentators indicated that they had no comments on the appraisal consultation document:

Department of Health
Pfizer

Ipsen Ltd – Response to Appraisal Consultation Document (ACD) consultation

11 May 2017

ID931 – Cabozantinib for previously-treated advanced renal cell carcinoma

Thank you for the opportunity to comment on the second ACD for the above appraisal. We note one area of the ACD (Section 4.4) where the Appraisal Committee has specifically identified the need for further clarification and note a second area (section 4.22) which we believe would benefit from more consideration. These two areas are:

- Section 4.4, which helpfully seeks confirmation as to where everolimus is used in the current treatment pathway.
  We have sought feedback from 15 leading, renal cell carcinoma-treating clinicians and found that, in fact, everolimus does not currently appear to be used in the second-line setting, despite recent NICE guidance (TA432[1]). In third line, usage also appears minimal. Further evidence is presented in Section 1 and Appendix 1.
- Section 4.22, which documents the Committee's concern that the utility values from the METEOR trial are too high and proposes that values from the AXIS trial should also be considered.
  On investigating this question we do not believe that AXIS is the most relevant set of alternative utilities, because they appear the least generalisable of the other plausible options. Accordingly, we outline those other options which have been used in recent appraisals in advanced RCC (aRCC). Further evidence is presented in Section 2.

We maintain that cabozantinib is cost-effective under the currently offered PAS discount of [redacted]%. However, we recognise the Committee's remaining uncertainty and the requirement to provide guidance on the most cost-effective use of NHS resources. Moreover, we are committed to making cabozantinib available to patients as soon as possible. To that end, we propose a revised Patient Access Scheme (PAS), whereby the simple discount is increased to [redacted]%. The effect of this discount is presented in Section 3.

In light of the real-world positioning of everolimus, coupled with the use of appropriate utility values and the increased PAS, cabozantinib is now demonstrably more cost-effective than the *appropriate* comparators in aRCC and represents good value for money for the NHS.

Section 1: Everolimus as a comparator

ACD Section 4.4 "[…]. *Given the recent changes in the recommendations for everolimus, and the clinicians' preference to use everolimus later in treatment, the committee appreciated that everolimus might be used after 1, but also after 2 or 3 previous treatments. The committee would welcome comments on the likely positioning of everolimus in the treatment pathway, following recent NICE guidance. The committee concluded that everolimus was a relevant option after 1 or 2 previous treatments alongside axitinib and nivolumab*."

In response to the committee's invitation for comments on the likely positioning of everolimus we have sought clinician feedback (Appendix 1) to understand whether everolimus is now

being used in the treatment pathway for the second (2nd) and/or third (3rd) line treatment of aRCC. Twenty clinicians were approached for detailed discussions with 15 responses received. Of these none positioned everolimus in the 2nd line setting, instead preferring either nivolumab or axitinib. Only one of the 15 clinicians stated that everolimus could considered as a possible option 3rd line, with the remaining 14 stating they use either axitinib or nivolumab 3rd line. Those 14 view everolimus as a fourth (4th) line option.

While we accept that the health system in Scotland is not directly related to that in England and Wales it may be useful for the Committee to consider the uptake of everolimus since it received SMC approval in November 2014, bearing in mind that axitinib has been funded in Scotland since November 2013. Significant usage would be reflected in the choice of everolimus as an appropriate comparator and current standard of care in SMC appraisals and this is not the case. In the recent SMC appraisal of nivolumab for the treatment of aRCC[2], clinical experts advised SMC that axitinib was the key comparator based on use in clinical practice. In addition, at the SMC's committee meeting held in public on 2nd May 2017, at which both cabozantinib and nivolumab (as a resubmission) for the treatment of aRCC were discussed, it was noted that axitinib was the appropriate comparator.

In addition to the clear position from the clinical community that everolimus is not used in the 2nd line setting, and only used 3rd line in only rare/exceptional circumstances, there are a further three important points which should also be considered:

1. The information submitted by NHS England during the re-appraisal of everolimus in aRCC (TA432) which stated[3]:

> "*16. NHS England now notes that the treatment pathway for patients with advanced and previously TKI-treated renal cancer may become more complicated with the potential inclusion of nivolumab for the TKI 1-prior and 2-prior populations, this being dependent on the currently running NICE appraisal. NHSE notes that the main evidence base for the benefit of nivolumab in renal cancer lies in a trial which compared nivolumab with everolimus. NHSE considers that any NICE recommendation for nivolumab within its licensed indication is likely to result in considerable use of nivolumab either as 2nd line treatment with axitinib being used 3rd line (as there is as yet no biological reason shown why axitinib should not work as well post-nivolumab as pre-nivolumab) or nivolumab used as 3rd line post-axitinib. Either of these scenarios would displace any potential availability of everolimus to 4th line therapy.*
>
> *17. NHS England notes that the relevance and importance of everolimus in the treatment of renal cancer has reduced, noting that the clinical expert input into the nivolumab appraisal clearly stated that there was clinical preference for the use of axitinib 2nd line rather than everolimus 2nd line. At present, the potential position of everolimus would be as 3rd line in the treatment pathway. This assessment may further change if nivolumab is recommended by NICE within its licensed indication and in which case everolimus would be positioned as a potential 4th line of treatment*."

This is entirely in line with the feedback Ipsen has received from clinicians regarding the place of everolimus in the treatment pathway. Since nivolumab for the treatment of aRCC has now received positive NICE guidance (TA417)[4] it appears that everolimus is generally viewed as a 4th line treatment, regardless of the availability of cabozantinib.

2. In the event the provisional recommendation for cabozantinib stands, it will endorse the illogical position whereby two drugs (axitinib and nivolumab), which are confirmed by the ACD to be less cost-effective than cabozantinib, will be available for use while the more cost-effective drug (cabozantinib) will be rejected simply because it is not cost-effective against a drug (everolimus) that is not used in clinical practice in these lines of therapy. We understand that this is the product of sequential single technology appraisals in the same therapy area, but it is nonetheless quite clearly a perverse outcome.

3. The decision to not recommend cabozantinib on the basis that is not cost-effective versus everolimus fails to take into account the fact that this appraisal is considering *two* distinct lines of treatment. If everolimus were accepted as the appropriate comparator in the 2nd line setting, it cannot at the same time also be the comparator in the 3rd line setting. That is, once everolimus is used in second line, the comparator for third line must be either nivolumab or axitinib. Similarly, if everolimus is considered to be the appropriate comparator in third line, then the treatments which precede it would have to be nivolumab or axitinib. In either case, cabozantinib becomes the most cost-effective option in whichever position is occupied by axitinib or nivolumab.

Section 2: Utilities

We appreciate that both the Committee and ERG had concerns about the utility values from the METEOR trial, citing general population utility estimates from Ara et al. 2010.[5] In considering the validity of the METEOR utility estimates, we note the statement in the first ACD (section 4.20) and second ACD (section 4.22) which acknowledged the potential impact of using the EQ-5D-5L[6] in METEOR. We would like to reiterate the findings of the Devlin et al. 2016 publication[6], which suggest that higher values with ED-5D-5L may be expected compared with EQ-5D-3L. This may at least partly explain the differences observed between estimates from METEOR and the age-specific general population utility values.

Both ACDs also state a preference for trial-based values which, in fact, is the case with the METEOR values. To substitute these for values from the AXIS trial introduces other potential complications, already acknowledged by the Committee and ERG. Indeed, we were requested to remove AXIS as a source of efficacy data in the network meta-analysis. We would have liked to understand the effect of prior cytokine use on patients' health, since in the axitinib appraisal (TA333)[7] separate values were provided for prior-cytokine and prior-VEGFR patients. Unfortunately, these values are redacted in the NICE documents and we have not been able to find them in any other publication. If utility estimates for the prior cytokine group differ from the utility estimates for the prior VEGFR-group, the proposed AXIS utility values which aggregate these two groups may not be appropriate.

Nonetheless, acknowledging the concerns regarding METEOR values, we have investigated which other utility values have most recently been used and accepted in appraisals in aRCC. These are detailed in Table 1.

Table 1: **Utility values for stable and progressed patients with aRCC**

	Value	**Source**	**Use in NICE appraisals**
Base case	PFS – 0.817 PD – 0.777	METEOR	
CheckMate Scenario	PFS – 0.76 PD – 0.70	CheckMate025, everolimus arm	Used in TA417[4] (published Nov 2016)
Sorafenib scenario	PFS – 0.76 PD – 0.68	Sorafenib utility for second line[8]	Used in TA432[3](published Feb 2017)
AXIS scenario	PFS – 0.69 PD – 0.61	AXIS	Used in TA333[7] (published in Feb 2015)

Key: PFS = Progression-Free Survival; PD = Progressed Disease.

In the event that other non-METEOR utility values are preferred by the Committee, we consider that the more plausible source for a set of alternative utilities is the everolimus arm of the CHECKMATE trial. That is, a utility value for PFS of 0.76 and for PD of 0.70. The

CHECKMATE trial is more in line with the METEOR trial both in its baseline population and to the extent that it reflects current practice in both prior and subsequent lines of treatment.

Section 3: Effect of Revised PAS

Tables 2 to 4 provide base case ICERs, with the addition of the new PAS and the various options for utility values.

Given the fact that all three comparator medicines have a PAS, we cannot be explicit in our statements of cost-effectiveness under every scenario. Nonetheless, we can say that unless the axitinib PAS exceeds [redacted]%, cabozantinib is now cost-effective when compared with axitinib even if the worst-case is assumed for the source of utility values (i.e. AXIS utilities). Cost-effectiveness in other scenarios will, of course, be improved versus axitinib. Cabozantinib's dominance over nivolumab is increased.

Table 2: Fractional polynomial model; pair-wise and incremental analysis of cabozantinib versus comparator using METEOR utilities - ITC-based analysis

Drug	Total costs				Total QALYs	Incremental versus cabozantinib					ICER versus cabozantinib			
	List price	PAS 1	PAS 2	PAS 3		List price	PAS 1	PAS 2	PAS 3	QALYs	List price	PAS 1	PAS 2	PAS 3
Cabozantinib	[redacted]													
Axitinib	[redacted]													
Everolimus	[redacted]													
Nivolumab	[redacted]													
Incremental Analysis	-	-	-	-	-	-	-	-	-	-	**ICER vs baseline**			
Everolimus	[redacted]													
Axitinib	[redacted]													
Cabozantinib	[redacted]													
Nivolumab	[redacted]													
PAS scenarios: [redacted]														

Table 3: Fractional polynomial model; pair-wise and incremental analysis of cabozantinib versus comparator using METEOR utilities - METEOR-based analysis

Drug	Total costs				Total QALYs	Incremental versus cabozantinib					ICER versus cabozantinib			
	List price	PAS 1	PAS 2	PAS 3		List price	PAS 1	PAS 2	PAS 3	QALYs	List price	PAS 1	PAS 2	PAS 3
Cabozantinib	[redacted]													
Everolimus	[redacted]													
PAS scenarios: [redacted]														

Table 4: Fractional polynomial model; pair-wise and incremental analysis of cabozantinib versus comparator – Utility scenarios

Drug	Total costs				Total QALYs	Incremental versus cabozantinib					ICER versus cabozantinib			
	List price	PAS 1	PAS 2	PAS 3		List price	PAS 1	PAS 2	PAS 3	QALYs	List price	PAS 1	PAS 2	PAS 3
METEOR Utilities														
Cabo - ITC	[redacted]													
Axi. - ITC	[redacted]													
Ever - ITC	[redacted]													
Nivo - ITC	[redacted]													
Cabo - METEOR	[redacted]													
Ever - METEOR	[redacted]													
TA432 Utilities														
Cabo - ITC	[redacted]													
Axi. - ITC	[redacted]													
Ever - ITC	[redacted]													
Nivo - ITC	[redacted]													
Cabo - METEOR	[redacted]													
Ever - METEOR	[redacted]													
CheckMate Utilities														
Cabo - ITC	[redacted]													
Axi. - ITC	[redacted]													
Ever - ITC	[redacted]													
Nivo - ITC	[redacted]													
Cabo - METEOR	[redacted]													
Ever - METEOR	[redacted]													
AXIS Utilities														
Cabo - ITC	[redacted]													
Axi. - ITC	[redacted]													
Ever - ITC	[redacted]													
Nivo - ITC	[redacted]													
Cabo - METEOR	[redacted]													
Ever - METEOR	[redacted]													

Key: cabo, cabozantinib, Axi, axitinib; Ever, everolimus; ITC, indirect treatment comparison; Nivo, nivolumab

PAS scenarios: [redacted]

Note: Cabozantinib remains dominant option compared to nivolumab under all utility scenarios.

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Appendix 1: Medical opinion – Position of everolimus in the treatment pathway

In response to the April 2017 Appraisal Consultation Document (ACD) for cabozantinib tablets for previously treated aRCC (ID931), Ipsen Limited sought expert medical opinion to address the Committee's request to clarify the positioning of everolimus in the treatment pathway, following its recent NICE Guidance (TA432).

"The committee would welcome comments on the likely positioning of everolimus in the treatment pathway, following recent NICE guidance. The committee concluded that everolimus was a relevant option after 1 or 2 previous treatments alongside axitinib and nivolumab." ACD Paragraph 4.4

We consulted 15 leading national and international clinical experts in aRCC representing practice from England and Wales Oncology Cancer Centres to ask what current practice was in their centres. Where permission was obtained, the clinicians are listed at the end of this document. Following initial discussions to clarify the positioning of everolimus, the clinical experts decided upon three treatment options which they consider to be their current practice, as per the below table.

Option A	**2nd line**		**3rd line**		**4th line**
Fail 1st line Pazopanib / Sunitinib	Nivolumab Or Axitinib	*Fail 2nd line*	Axitinib Or Nivolumab	*Fail 3rd line*	Everolimus
Option B	**2nd line**		**3rd line**		**4th line**
Fail 1st line Pazopanib / Sunitinib	Nivolumab	*Fail 2nd line*	Axitinib Or Everolimus	*Fail 3rd line*	Everolimus Or Axitinib
Option C	**2nd line**		**3rd line**		**4th line**
Fail 1st line Pazopanib / Sunitinib	Nivolumab	*Fail 2nd line*	Axitinib	*Fail 3rd line*	Everolimus

Nine chose Option A, one chose Option B and five chose Option C.

This suggests that everolimus is not routinely used after one or two previous treatments in patients with advanced or metastatic renal cell carcinoma.

Fourteen of fifteen clinical experts confirmed that everolimus would generally only be used in the 4th line treatment setting following progression upon sunitinib or pazopanib, nivolumab and axitinib.

This document has been created and reviewed in consultation with clinicians at the following NHS Hospitals:

Clinician	Hospital
[redacted]	Bristol Haematology and Oncology Centre, Bristol
[redacted]	Addenbrooke's, Cambridge
[redacted]	Royal Marsden, London
[redacted]	Velindre, Cardiff
[redacted]	St Luke's Cancer Centre, Guildford
[redacted]	St George's, London
[redacted]	Queen Elizabeth, Birmingham
[redacted]	Charing Cross, London
[redacted]	Guy's and St Thomas', London
[redacted]	Royal Sussex County, Brighton
[redacted]	Leeds Cancer Centre, Leeds
[redacted]	Singleton, Swansea

In addition to the above three clinicians provided a response but did not wish to be named in the document (one each for options A, B and C).

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Response to the Appraisal Consultation Document 2 (April 2017): Cabozantinib for previously treated advanced renal cell carcinoma [ID931]

Kidney Cancer Support Network Statement

In a second Appraisal Consultation Document (April 2017), the NICE technology appraisal committee have again not recommended cabozantinib for use within its marketing authorisation for the treatment of advanced renal cell carcinoma (RCC) in adults after vascular endothelial growth factor (VEGF)-targeted therapy. This is despite cabozantinib's proven effectiveness at prolonging the life of kidney cancer patients by 4.9 months compared to everolimus in the METEOR trial, and impressive progression-free survival benefit in patients with spread to their bones, reducing the risk of death by 46% compared with everolimus in patients with bone metastases. In addition, cabozantinib has demonstrated clinically significant benefit over everolimus in all three clinical trial efficacy endpoints, namely progression-free survival, overall survival and response rate. This finding is unprecedented in recent clinical trials with RCC agents.

The Kidney Cancer Support Network's response to the second cabozantinib ACD has been informed by the views of advanced kidney cancer patients who are taking cabozantinib as part of a clinical trial or through a Managed Access Programme in the UK.

1. Treatment options in the second- and third-line settings

Cabozantinib was compared to everolimus in the METEOR trial, and was proven to be a clinically effective and well-tolerated drug, leading to its designation as a **'promising innovative medicine' for advanced RCC by the Medicines and Healthcare products Regulatory Agency (MHRA)** last year. Cabozantinib is positioned as a second-line treatment for advanced RCC after VEGF-targeted therapy. The ACD recognises that cabozantinib is more effective than everolimus, and probably more effective than axitinib (the two drugs have not been compared directly in a randomised controlled clinical trial), although it is associated with more adverse events. The ACD states, "….despite new treatments recently being recommended by NICE, there remained limited treatment options and an unmet clinical need for some people with advanced renal cell carcinoma."

The ACD mentions the three treatment options available to advanced RCC patients in the second- or third-line setting as recommended by NICE guidance, namely nivolumab, everolimus and axitinib. However, it seems that in clinical practice, usually nivolumab or axitinib are given in the second-line setting, and if patients fail second-line treatment they progress on to the alternative drug (either nivolumab or axitinib). Everolimus appears to be reserved for fourth-line treatment when all other options have failed.

This situation is confirmed by the fact that, although everolimus is now available for routine clinical use in NHS England in the second-line setting or later, we could only find 2 patients who are currently taking the drug from our Kidney Cancer Support Network community of over 1,000 kidney cancer patients. This is anecdotal evidence that, although everolimus is now recommended after 1 or more lines of VEGF-targeted therapy (which includes TKIs), everolimus does not appear to be a "relevant option after 1 or 2 previous treatments alongside axitinib and nivolumab" as stated in the ACD, and is not being used in routine clinical practice on a regular basis. This provides real world evidence on the positioning of everolimus in the treatment pathway for advanced RCC in the fourth-line setting after failure of nivolumab and axitinib.

Further to the recent NICE guidance following the Cancer Drugs Fund reconsideration of everolimus, the ACD concludes that "everolimus is a relevant option after 1 or 2 previous treatments alongside axitinib and nivolumab". However, we would question this statement and suggest patients seek a second opinion if they are prescribed

everolimus in the second-line setting (unless nivolumab is contra-indicated due to an autoimmune condition), particularly when nivolumab has been proven to be more effective and better tolerated:

> *"I was on pazopanib …… when my oncologist determined that it was starting to fail. At that point I was advised that everolimus was to be made available to me …….. Initially side effects were minimal, however about a month [sic] I started to get very bad mouth ulcers, which took a few weeks to clear up, fatigue and tiredness. Also experienced anaemia and had 2 blood transfusions. I suffered from nosebleeds, mainly when blowing my nose! Lung condition didn't help and was experiencing dry cough and breathlessness as well. Experienced lots of indigestion also had mild doses of feeling shaky and shivery. Ct scan showed that everolimus was struggling and the decision to try for Nivolumab taken in Feb/March 2016……This new drug has enabled me to lead as normal a life as possible; side effects have been minimal although I have lost some weight (around 6lbs). I do have some itchiness on lower legs and arms but this is dealt with by taking standard over the counter antihistamines. I am finding Nivolumab kinder on my system than Everolimus previously."*

We appreciate the cost per QALY considerations implicit in these decisions; however, clinicians should have the ability to choose the most effective treatments for individual patients from those available, and **without cabozantinib, the clinician's choice of treatment is seriously compromised**. Without treatment alternatives in the second-line setting and later, most patients will face disease progression. A choice of treatment is paramount for the effective management of the progression of this disease and maintenance of quality of life:

> *"Whilst I have not had direct experience of taking Cabozantinib as I am still responding to Pazopanib, I have read both the clinical trial reports and real world patient experience. I believe that this would form a useful addition to the portfolio of drugs available to clinicians and will be especially useful for those patients with bone metastasis. The addition of more potential drugs would introduce more competitive pricing between suppliers."*

Current second- and third-line treatment options are not effective for everyone, and can be difficult to access. Undue restrictions in accessing cabozantinib would simply add unnecessary additional burden to patients with a terminal diagnosis. Having more choice in the second-line setting and beyond would enable patients and oncologists to individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient. Cabozantinib will also address the massive unmet need for treatment options in the third-line setting and later.

The following statements are from a patient carer and two patients talking about the importance of having choice of treatment in the second- and third-line setting:

> *"I have used sutent, pazopanib and now axitinib for almost five years. When Axitinib is done, I want to be able to turn to Cabozantinib as I have a bone met. Please give me the choice."*

> *"In response to cazantinib* [sic] *not being approved by NICE, this is a drug that had been mentioned to me as a next step to help keep my kidney cancer at bay, it could give me valuable extra time with my two young daughters aged 4 & 2 years old. Without this medication my girls could lose their mummy too soon & they don't deserve that. This could help so many people live longer; everybody is worthy of that chance. Please think again."*

2. Effect on bone metastases

Although not discussed in the ACD, there is anecdotal evidence that cabozantinib is particularly effective against bone metastases. Kidney Cancer Support Network has heard from a number of patients who confirm this activity, and clinicians are also recommending cabozantinib specifically for patients with bone metastases.

Cabozantinib is the first tyrosine kinase inhibitor to act on multiple tyrosine kinase receptors, including c-MET, VEGF2, AXL and RET. Its c-MET activity may explain its effectiveness against bone metastases, since MET appears to be an important growth factor in the bone microenvironment. The following statement from the husband of a patient highlights the importance to patients of cabozantinib's efficacy against bone metastases:

> *"…..CT and MRI results …… yesterday gave excellent news confirming her 10-off* [sic] *spinal bone Mets being reported stable. This is a great result having halted the disease given she only recently commenced her Cabozantinib treatment on 23/11/16; at a time when the bone progression appeared*

aggressive, i.e. with 3 lytic bone Mets being reported by CT scan on 21/10/16 increasing to 10 Mets reported from an MRI scan on 19/12/16.

"……. the immediate issue was rapidly developing bone mets (i.e. crocodiles nearest the boat, so to speak). Since Cabo was the only 'available' agent that has a pathway able to specially target bone Mets, then this became OUR first choice …... Note: we had overturned the originally advised preference ranking order for Axitinib, Nivolumab and lastly Cabozantinib."

Bearing this in mind, if the committee is minded not to approve cabozantinib, the **Kidney Cancer Support Network urge NICE to reconsider cabozantinib for the Cancer Drugs Fund (CDF) while further survival data are collected from the cohort of patients with bone metastases** to provide further evidence to support this effect in advanced RCC patients. With around 5,000 patients diagnosed with advanced RCC per year, this disease is designated a rare cancer. This should be considered when setting time limits for the collection of survival data, and the 24-month period, as specified in the CDF SOP for collection of addition evidence to support this observation, should to be extended for the small population of patients who have spread to their bones.

The following statements are from an advanced RCC patient and the wife of an advanced RCC patient, and demonstrate how well informed patients are about the effectiveness of cabozantinib against bone metastases:

"Three years after a nephrectomy for RCC, I became aware of bone pain in my femur, which subsequently broke due to a single site metastasis that had become so large there was very little bone remaining. Following surgery, in December 2014 I was started on Sunitinib. At that time I had no other mets, and that is still the case, so Sunitinib has been successful in preventing spread, however, it has had no measurable impact in reducing the bone met, over 2 years later. Sunitinib, like the other currently approved drugs is not greatly effective on bone mets. However Cabozantinib has clear data demonstrating that it can be highly effective in shrinking and removing altogether bone metastases. For me, that could mean achieving NED, which result in a big saving in no requiring further expensive treatment [sic].

"This is the only drug currently available that is so effective on bone mets and therefore for patients like myself it is essential that this drug is approved for use at least in the second line setting to offer real hope to patients with bone metastases. I would therefore urge NICE to approve this new drug as soon as possible"

"My husband has run out of options for surgery on his maxilla area without it compromising his eye. His other secondaries are kept under control and after nearly 7 years he is stable. He needs a drug, which works on bone metastases as none of the current drugs appear to have any measurable success and sadly kidney cancer often goes to hips and spine as well as other areas."

3. Cost effectiveness

We are disappointed that **yet again another drug for advanced RCC has been declined on the basis of the use of an unsuitable health economic assessment for small patient groups (a rare cancer):** Incremental Cost Effectiveness Ratio (ICER) per Quality Adjusted Life Year (QALY) is used in assessment of cost effectiveness for all cancer drugs and is based on a threshold of an ICER per QALY of £30,000, set in 1999 (although recently a threshold of £50,000 has been quoted for life-extending drugs). These assessments have time and again been shown to be unfair to many rare cancer patient groups, denying these patients access to life-prolonging treatments during a desperately difficult time for both themselves and their families.

We understand that cabozantinib is expensive, and we appreciate the budgetary implications, but nonetheless NICE and the manufacturers must negotiate and find a way to make this new and innovative drug available to the patients who need it; failure to do so would be seen as failure of professional competence. NICE and the manufacturer need to think outside the box to agree an alternative funding process, and work collaboratively to negotiate an acceptable patient access scheme to ensure kidney cancer patients who need it can have access to this latest clinically effective drug.

"My dad's consultant has suggested that should nivolumab stop working then this would be the next step. He specifically mentioned that Cabozantinib was more effective on bone mets than other lines of treatment, which we took as a positive since dad has mets on his spine. If this wasn't an option I think we'd be at the end of the line as dad has had IL2, sutent and axitinib prior to nivolumab. It really would be a matter of life and death and to know that there is something there that could extend life but wasn't

available would be heart breaking. I know there has to be assessments around cost versus impact, but given dad's history it might have been felt that nivolumab wouldn't work when it has - he's been on it for almost a year now. Some weren't as lucky as dad and missed nivolumab. I'd hate to see this happen again."

Thank you for allowing the Kidney Cancer Support Network to take part in this single technology appraisal. We welcome the opportunity to put forward the views of our Kidney Cancer Support Network patient community for this important health technology appraisal of cabozantinib in advanced renal cell carcinoma.

Kidney Cancer UK hopes Cabozantinib will be recommended by NICE in England and Wales as a second-line treatment of advanced kidney cancer.

Kidney Cancer UK is very disappointed to hear that at the midpoint of the Single Technology Appraisal (STA) of cabozantinib, NICE is considering NOT recommending its use within the NHS. Having a variety of targeted therapy options is vital for patients with advanced kidney cancer; providing hope and extra months and years of life. Different patients respond positively to different medicines. Providing a variety of therapeutic options should also help patients find a medicine that works for them. Adding cabozantinib to the second, third, fourth-line treatment options and beyond provides an option that could work really well for some patients; making kidney cancer a chronic disease rather than fatal.

An example of cabozantinib working well, is described by David Chessum, who shared his experience with us on a video for supporters of Kidney Cancer UK. Please view his video for more details. https://www.youtube.com/watch?v=9asTUb1CZRU His experience of cabozantinib has been very positive: his quality of life has improved and he no longer has to deal with severe diarrhoea, a side-effect of his previous drug regime. Cabozantinib has given him a much better quality of life, something we hope will be strongly considered during the NICE appraisal.

One issue that has arisen from the recently released Appraisal Consultation Document (ACD) is the lack of guidance and standardisation for doctors regarding the sequence of second-line treatments onwards. Currently axitinib, nivolumab and everolimus are recommended by NICE as second-line treatments. Sunitinib and pazopanib are recommended as first-line treatments. In reality, the treatments given as a second-line treatment and beyond are very varied: the recommended first-line drugs are often given as fifth-line drugs and some second-line drugs are rarely prescribed at all. The 2016 Kidney Cancer UK annual survey requested information about which drugs had been taken by each responder. 111 people took the survey, 34 had taken medicine for advanced kidney cancer.

- The first-line drugs were split fairly evenly between pazopanib and sunitinib, 1 person each took interleukin, everolimus (trial) and sorafenib (trial).
- 13 people went on to take a second-line drug; 7 took axitinib, 5 took either the other first-line drug (pazopanib or sunitinib), one advanced to interleukin 2.
- 7 people advanced to a third-line drug, 5 of which took nivolumab, 1 pazopanib and 1 axitinib.
- 1 person had taken a fourth-line drug, which was sunitinib (a first-line drug).
- 1 person advanced to a fifth-line drug (axitinib).

The data from our survey indicated that everolimus was not taken once as a second-line or beyond drug. Only once was it taken as a first-line treatment during part of a clinical trial. Everolimus is the drug that cabozantinib has been compared to in the METEOR clinical trial so its use is of relevance in the STA. Everolimus was previously available on the old Cancer Drug Fund and Kidney Cancer UK is pleased that everolimus (an mTOR inhibitor) has recently been recommended by NICE through its rapid appraisal scheme. Everolimus is important as it offers an alternative way of attacking kidney cancer tumour cells compared to TKI's or immunotherapy, but we would like to ask why it is not being recommended by doctors for use on the NHS. ~~Perhaps now that everolimus has been recommended for use by NICE, rather than being on the cancer drug fund, we may see more wide spread use as a second-line treatment?~~

We certainly would welcome more research and guidelines in the area of the sequencing of second-line treatments and beyond. We understand that many doctors use the EAU (European association

of urology) guidelines but there are no firm conclusions on the sequencing of drugs beyond second-line treatments. "No firm recommendations can currently be made as to the best sequence of targeted therapy, beyond the recommendation that VEFG-targeted therapy should be used for patients with good- and intermediate-risk disease."[1]. We feel this issue should be addressed in the near future and perhaps a UK-based set of guidelines should be established, due to the variations in NICE recommendations compared to Europe drug licencing.

We sincerely hope that cabozantinib is recommended by NICE in England and Wales: the wider the choice of available drugs the better potential outcomes for patients with advanced kidney cancer. Cabozantinib has been shown to provide a tolerable range of side-effects that can benefit some patients quality of life. This is invaluable. We also envisage an era of medicine where combinations of different targeted therapies are utilised and specific medicines are given to people with appropriate genetic profiles, to produce even better survival rates; we feel that cabozantinib could be very useful in this approach. We hope that the area of multiple second-line therapies continues to evolve and expand within the UK, as it is in other countries across the world.

1. http://uroweb.org/wp-content/uploads/10-Renal-Cell-Carcinoma_LR.pdf

Renal cell carcinoma (advanced, treated) - cabozantinib [ID931]
Comments from Kidney Research UK, 15th May 2017

NICE has stated Cabozantinib is **not** recommend by NICE within its marketing authorisation for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF) targeted therapy, but has acknowledged that Cabozantinib improved progression-free survival compared to everolimus. However, (Section 4.30) NICE acknowledges that Cabozantinib is an innovative treatment. Clinical experts stated that because of the product's multi-targeted approach, Cabozantinib would likely have additional benefits for some patients. They also stated that the product would be highly valued in patients whose disease is resistant to standard tyrosine kinase inhibitors (TKIs) and may not have responded to Nivolumab and that Cabozantinib could fulfil an unmet need in this group of patients. **Kidney Research UK support this statement as clinicians are best placed to fulfil the clinical needs of patients and this offers patients improved progression-free survival compared to those treated with standard therapy .**

(Page 21) **Current Practice**

The committee stated they were aware there remained limited treatment options and an unmet need for people with advanced renal cell carcinoma. Especially those patients whose disease is resistant to standard TKIs and have not responded to Nivolumab .**We support this statement as treatment options are limited and patients have the right to be given a choice of a treatment that is more effective than everolimus and axitinib and are willing to accept more adverse events**

Clinically relevant sub groups of patients

The committee accepted that it would consider Cabozantinib for a patient population where people had had one or two previous treatments as a whole.

We fully support this statement.

Section 5.1

The Department of Health and Ipsen have stated that Cabozantinib will be made available to the NHS within the parameters of a confidential patient access scheme (PAS) which makes Cabozantinib available with a discount **We are heartened to see that the product will be available for a sub group of patients and would like to see if being made available for all patients who would derive most benefit.**

NHS England comment re place of everolimus in the treatment of advanced/metastatic renal adenocarcinoma

1. The two established treatment options as 1st line systemic therapy are the multi-targeted tyrosine kinase inhibitors, sunitinib and pazopanib (both include VEGF inhibition). These are either/or options as 1st line treatment.
2. Axitinib is NICE-approved after 1st line treatment.
3. Nivolumab is NICE-approved as either 2nd or 3rd line treatment.
4. Everolimus is now NICE-approved, its license being after VEGF-targeted treatment.
5. NHS England is shortly to consult on a treatment algorithm which sets out the following (active consideration of best supportive care occurs with each therapy):
    - 1st line: sunitinib or pazopanib
    - 2nd line: axitinib or nivolumab or everolimus
    - 3rd line: axitinib or nivolumab or everolimus depending on what was used before as 2nd line treatment
    - 4th line: axitinib or nivolumab or everolimus depending on what was used as 2nd and 3rd line treatment.
6. Since all the 2nd/3rd/4th line treatment options have differing modes of action, there is biological plausibility in for example everolimus being active after nivolumab or axitinib. This biological plausibility justifies the sequential set of treatment options in the algorithm as stated above.
7. Just because the algorithm states 4 potential lines of treatment does not mean that NHS England expects all patients to proceed from 1st line to 4th line. Only a minority of patients will be fit enough and motivated enough to explore all 4 options.
8. Clinicians inform NHS England that everolimus is used less than the other options of axitinib and nivolumab.
9. Cabozantinib is a multi-targeted TKI, sharing some common targets as the other TKIs but also has some novel targets. There is biological plausibility that it would show activity in patients treated with other TKIs and its main registration trial included patients previously treated with VEGF-targeted treatments and the programmed death 1 receptor or its ligands.
10. If NICE recommends the use of cabozantinib (this being an optimised recommendation), NHS England would see it as being an additional options as 2nd/3rd/4th/and even 5th line treatment. NHS England recognises that the number of patients diminishes significantly with each line of therapy on account of both disease-orientated reasons and patient choice and also understands that one patient may tolerate one TKI better than another.

[redacted] May 2017

[redacted]

Centre for Experimental Cancer Medicine
Barts Cancer Institute
Queen Mary University of London
Old Anatomy Building
Charterhouse Square
London, EC1M 6BQ

15 May 2017

Dear NICE,

I'm writing on behalf of the National Renal cancer clinical studies group. We were disappointed that cabozantinib was rejected. The most recent European guidelines (Powles et al) state that both cabozantinib and nivolumab have superseded other drugs, such as axitinib and everolimus in this space. Therefore from a clinical perspective, cabozantinib should be used preferentially over axitinib and everolimus. Axitinib and everolimus can be considered to have similar efficacy, with no clear survival benefit, which is not the case for cabozantinib or nivolumab. The renal cancer space has become complex due to the sequential availability of drug and NICE making prospective but not retrospective assessment of agents.

The CSG respects the NICE process, and welcome cost-assessment exercises to ensure all aspects of healthcare are treated with parity. Nevertheless, cabozantinib is one of only 2 agents to show clear survival benefit in renal cancer, and therefore it should be potentially prioritised over other agents. I hope this is helpful and would be very happy to discuss or clarify over the telephone or in person.

Yours Sincerely,

[redacted]

[redacted]

1 - European Association of Urology Guidelines for Clear Cell Renal Cancers That Are Resistant to Vascular Endothelial Growth Factor Receptor-Targeted Therapy.
Powles T, Staehler M, Ljungberg B, Bensalah K, Canfield SE, Dabestani S, Giles RH, Hofmann F, Hora M, Kuczyk MA, Lam T, Marconi L, Merseburger AS, Volpe A, Bex A.
Eur Urol. 2016 Nov;70(5):705-706. doi: 10.1016/j.eururo.2016.06.009. Epub 2016 Jun 24.

Comments on Cabozantinib ACD for RCC 2017

Whilst I cannot comment of the technical assessment of cost effectiveness I will make a number of observations from a clinical perspective.

1. From a practical point of view the main comparators for cost effectiveness is really Axitinib or Nivolumab. In the vast majority of patients Everolimus will be used as a third / fourth line therapy after failure of Cabozantinib/Nivolumab/Axitinib.
2. Given the above the key economic comparator is not Everolimus but Axitinib and/or Nivolumab.
3. In reality most patients will be considered for 2 TKIs (first line therapy and one other) and Nivolumab – the order of second TKI and Nivolumab will vary according to various clinical factors but certainly, I would consider the benefits of three lines of TKI (Sunitinib/Pazopanib, Cabozantinib and Axitinib) are likely to be less than 2 lines and Nivolumab. It would therefore be reasonable to restrict clinical choice to 2-lines of TKI rather then the potential to have 3-lines.
4. Although I do not have access to the commercial discount figures I imagine Everolimus has been approved as a result of a substantial discount that happened after the approval of Nivolumab. It seems that Cabozantinib is now being compared with reduced price of Everolimus whereas Nivolumab was compared with the full price – this potentially leads to the rejection of Cabozantinib and the acceptance of Nivolumab – this seems illogical since as I understand it, the NICE appraisal suggests Cabozantinib is more cost effective than Nivolumab?

Robert Hawkins

10 May 2017

Comments on the ACD Received from the Public through the NICE Website

Role	NHS Professional
Other role	Consultant Medical Oncologist
Organisation	
Location	England
Conflict	Yes
Notes	I have accessed cabozantinib as part of the expanded access program & have agreed to speak at a meeting sponsored by Ipsen.

Comments on the ACD:

As a Consultant Medical Oncologist working with a speciality in metastatic renal cell cancer I was excited by the data for cabozantinib in improving patients survival as identified in you executive summary. There is a great need for renal patients who have failed first line treatments to access the best options - in the second line setting (in my opinion) this is now cabozantinib or nivolumab (as per ESMO Guidelines). The patients receiving cabozantinib are patients who have an opportunity for more rapid responses (in comparison to nivolumab or everolimus) & certainly is my preferred option in this patient population. A rechallenge with a different biological is essential & responses seen with Cabozantinib is proven to be of more benefit than everolimus. Renal cell cancer patients need every opportunity to gain benefit from the licenced treatments available.