NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

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:
   - Eisai
   - Kidney Cancer Support Network
   - *Department of Health – had no comments*

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

4. **ERG critique of company response to the ACD**

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

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

Single Technology Appraisal

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

Type of stakeholder:

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.

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.

Comment number	Type of stakeholder	Organisation name	Stakeholder comment Please insert each new comment in a new row	NICE Response Please respond to each comment
1		Eisai Limited	**Eisai does not agree that the design and size of the HOPE 205 trial precludes its results from forming a robust basis for decision-making.** This study was not pre-planned as a pivotal trial, but the results were so compelling that Eisai met with the regulators to discuss the possibility of this study supporting a marketing authorisation. The results of the study were also considered by the Committee for Medicinal Products for Human Use (CHMP) to be of major interest to the European Community on grounds of public health and therapeutic innovation, warranting their submission via the accelerated assessment procedure. The CHMP subsequently opted to grant a full marketing authorisation for the combination rather than a conditional approval requiring a post-approval efficacy study. No post-approval measures regarding evaluation of efficacy were required to be included in the risk management plan. From this, it should be understood that the European body tasked with the evaluation of benefit/risk of therapeutic agents intended for marketing in the EU (the CHMP), has concluded after an extensive review of the data over a 7-month period that the risk/benefit ratio of the combination is conclusive. Data from Study 205 show that lenvatinib in combination with everolimus was highly active in terms of progression free survival (PFS) and objective response rate (ORR) in patients with metastatic renal cell carcinoma (RCC). It is important to note that the PFS results by investigator assessment were corroborated by retrospective blinded independent assessment. In addition, there was a trend towards improved overall survival (OS) which was maintained in two additional OS analyses. Although a number of single agents, including an anti-PD-1 inhibitor, have recently been recommended by NICE for use in this RCC patient population, these agents will not be suitable for all patients. There is still an unmet need, particularly for those patients who are symptomatic with aggressive tumours who would benefit from a combination regimen for a rapid and high response. Given that the lenvatinib and everolimus combination is currently cost effective versus these agents, Eisai believe that it should be given “conditional approval” for entry into the Cancer Drugs Fund to allow for the opportunity for additional data to be collected to confirm the efficacy	Thank you for your comment. The committee concluded that, given the clinical evidence to date, the results of HOPE 205 need to be interpreted with caution, mainly because the trials was small. Please see sections 3.5, 3.9 and 3.10 of the FAD.

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			demonstrated in the HOPE 205 study. We are keen to work with NICE to address any uncertainties they believe exist with the currently available data in respect to relative treatment effectiveness and duration of treatment. The company does not currently have any ongoing studies in this second-line indication. However, Eisai are in the very early stages of considering a large prospective study to capture further information around safety and quality of life with the aim to have results by 2020. It would be possible to include efficacy outcome measures in this trial and Eisai would like NICE to consider whether this type of study would be sufficient to address the relevant uncertainties to gain a recommendation to go into the Cancer Drugs Fund.	
2		Eisai Limited	**Eisai disagree that there is uncertainty around the optimal dose of lenvatinib.** Eisai acknowledges that dose modifications occurred during the HOPE 205 study with a median daily dose of 13.6 mg. Eisai does not believe that this represents an uncertainty around the optimal dose. Dose modification and interruption guidelines are available in the Summary of Product Characteristics (SPCs) of the other tyrosine kinase inhibitors (TKIs) used in advanced RCC. This represents the general approach when using these medicines in RCC ie using the recommended dose to induce tumour regression and then modifying or interrupting the dose to manage the tolerability for the patient, thereby maximising the overall time on treatment. This flexible dosing approach tailors the dose to the needs of the patient rather than indicating an uncertainty around the optimal dose. As stated in section 3.6 of the ACD, Eisai are conducting a clinical trial comparing the effects of a lower starting dose of 14mg of lenvatinib with the current recommended dose of 18mg. However, the objective of this study is to explore whether it is possible to achieve the same efficacy with a slight improvement in tolerability. The company thinks this is unlikely but is studying this in order to provide further information on benefit/risk of differing starting doses.	Thank you for your comment. The committee noted your view that the trial comparing the recommended dose of lenvatinib (18 mg) with a lower dose (14 mg) was to assess whether the same efficacy can be achieved with improved tolerability. Please see section 3.6 of the FAD.
3		Eisai Limited	**Eisai do not agree that the differences in baseline characteristics between treatment groups in the HOPE 205 study impact the outcome of the study.** It is important to note that the CHMP assessed that the imbalances in baseline characteristics between treatment groups were not of sufficient magnitude to impact the outcome of the HOPE 205 study. *Tumour burden* With respect to the differences in baseline characteristics related to tumour burden, as part of a	Thank you for your comment. The committee noted that the tumour burden was greater in patients randomised to lenvatinib plus everolimus than in those randomised to everolimus alone. The ERG did not consider that any individual difference in the characteristics

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			response to the EMA during the regulatory process, Eisai conducted analyses using baseline tumour burden (number and site of metastases) as a potential confounding factor for both PFS and OS. Results of these analyses are consistent with the original ITT analyses, indicating that baseline tumor burden had no meaningful impact on the PFS and OS results and any observed imbalance did not impact the interpretation of the primary results. These results were accepted by the CHMP. <u>Progression-free survival</u> When the number of baseline metastases (0,1,2 or ≥3) was added to the analysis of investigator assessed PFS as a covariate in the Cox regression model (data cutoff date of 13 June 2014), the estimated HR and 95% confidence interval (CI) for the combination arm compared with the everolimus arm (HR=0.426 [95% CI: 0.252, 0.720]) from the model was consistent with that of the original ITT analysis (HR=0.401 [95% CI: 0.239, 0.675]). Similarly, the HRs and CIs for the PFS subgroup analysis between the combination and everolimus arms by site of metastasis were all consistent with that for the overall population, and favoured the combination arm across all subgroups. These results demonstrate that the status of and the imbalance in baseline metastases had no meaningful impact on the overall conclusion for the PFS result. <u>Overall survival</u> Similar to the results for PFS, when the number of baseline metastases was included as an additional covariate in the analysis of OS using the Cox regression model (data cutoff date of 31 July 2015), the estimated HR and 95% confidence interval (CI) for the combination arm compared with the everolimus arm (HR=0.641 [95% CI: 0.389, 1.056]) from the model were consistent with that of the original ITT analysis (HR=0.588 [95% CI: 0.359, 0.965]). In addition, the HRs and CIs for the combination arm compared with the everolimus arm by site of metastasis were all consistent with that for the overall population, and favoured the combination arm across all subgroups. *Previous therapy* With respect to differences in baseline characteristics related to previous treatment, post-hoc subgroup analyses conducted as part of EMA responses during the regulatory process have shown that the combination arm demonstrated superior efficacy compared with everolimus in Study 205, regardless of duration of prior anti-VEGF therapy received. These results suggest that prior anti-VEGF therapy had no meaningful impact on the overall conclusion for PFS and OS	at baseline would modify the effect of the study treatment, but that all differences taken together may have introduced bias in favour of lenvatinib plus everolimus. The committee agreed that the reported results may have overestimated the effectiveness of lenvatinib plus everolimus. Please see section 3.10 of the FAD.

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			results and support the opinion of the clinical expert that it is debatable that length of prior treatment is a prognostic factor. Progression-free survival When the duration of treatment with prior VEGF-targeted therapy was added to the analysis of investigator assessed PFS as a covariate in the Cox regression model (data cutoff date of 13 June 2014), the estimated HR and CI for the combination arm compared with the everolimus arm (HR=0.433 [95% CI: 0.252, 0.742]) from the model was consistent with that of the original ITT analysis (HR=0.401 [95% CI: 0.239, 0.675]). Overall survival Similar to the results for PFS, when the duration of treatment with prior VEGF-targeted therapy was included as an additional covariate in the analysis of OS using the Cox regression model (data cutoff date of 31 July 2015), the estimated HR and 95% confidence interval (CI) for the combination arm compared with the everolimus arm (HR=0.630 [95% CI: 0.381, 1.040]) from the model were consistent with that of the original ITT analysis (HR=0.588 [95% CI: 0.359, 0.965]). The results for PFS, OS and objective response rate (ORR) in the HOPE 205 study favoured the combination arm over the everolimus monotherapy arm regardless of which prior VEGF-targeted therapy was used. An ad hoc subgroup analysis by prior type of treatment showed that results favoured the combination arm over everolimus regardless of which prior VEGF-targeted therapy was used, with nearly identical HRs for investigator assessed PFS (data cutoff date of 13 June 2014) in both subgroup categories (sunitinib, HR=0.356; other VEGF-targeted therapies, HR=0.350; *P*=0.003 and *P*=0.017 for the 2 subgroups, respectively). The HRs for OS for the sunitinib and other-VEGF subgroups were 0.532 and 0.639, respectively, and favoured the combination over everolimus. Similar results were seen for ORR by prior therapy ie in patients who received prior sunitinib, the ORR was 41.7% for the combination arm versus 3.6% versus the everolimus arm and for those who received different prior VEGF-targeted therapy, the ORR again favoured the combination arm (46.7%) compared with 9.1% for everolimus. It is also important to note that a separate Phase III trial of sunitinib versus pazopanib in the first-line treatment of advanced RCC showed similar efficacy between these 2 agents, with a median PFS of 8.4 months for pazopanib (95% confidence interval [CI], 8.3 to 10.9) and 9.5 months for sunitinib (95% CI, 8.3 to 11.1) and an HR of 1.05 (1). This trial demonstrates that there is little difference in efficacy among anti-VEGF TKI agents in the first-line setting. Therefore, it is highly unlikely that a particular first-line anti-VEGF agent would have a differential effect on efficacy once	

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			a patient enters the second-line setting. **Reference:** 1. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. NEJM 2013;369: 722-731	
4		Eisai Limited	**The lenvatinib plus everolimus combination has a manageable safety profile.** It is important to note that, as stated on the slides presented at the first NICE committee meeting, patient and professional feedback obtained during this NICE STA to date has noted that this combination does have more side effects than the individual treatments, but that these were considered manageable. Despite the availability of single agents in this setting, there is still an unmet need, particularly for those patients who are symptomatic with aggressive tumours (ie those with a high tumour growth rate).These patients need a rapid and high response and the rationale behind the combination was to start on the recommended dose to induce optimal tumour regression followed by individual adjustments to manage tolerability. This flexible dosing approach tailors the dose to the needs of the patient and maximises the time on treatment. Safety analyses of the HOPE 205 study have showed that lenvatinib as a combination therapy, has a predictable and manageable safety profile. In general, the overall adverse event (AE) profile for combination lenvatinib/everolimus was as expected for these classes of compounds and was consistent with the safety profiles of lenvatinib and everolimus as monotherapy. Based on an initial analysis of the AEs that were observed, Eisai considers there to be 4 potential worsening safety signals for combination therapy compared with either or both monotherapy agents: diarrhoea, hypercholesterolemia, hypothyroidism, and increased blood TSH. All of these can be managed with adequate monitoring, dose reduction and interruption, and prompt medical treatment.	Thank you for your comment. The committee concluded that lenvatinib plus everolimus has a high burden of adverse events and is not well tolerated, even by patients who are relatively fit compared with the average person who would have this treatment in clinical practice. Because of this, the committee agreed, it was important to consider performance status in the decision-making. Please see section 3.13 of the FAD.
5		Eisai Limited	**Eisai do not agree that the summary of the cost effectiveness evidence is a reasonable interpretation of the evidence for the reasons cited below:** **The utility values used in the model do reflect the quality of life appropriately.** The wording currently in the ACD does not fully reflect the methodology used by Eisai in the company submission to estimate the impact of adverse events on health-related quality of life. It is important to note that the company's estimations incorporate the average duration of each	Thank you for your comment. The revised utility decrement for lenvatinib plus everolimus remained small because it did not correlate with the observation in HOPE 205 that all patients who had lenvatinib plus everolimus had an adverse

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			adverse event, taken directly from the HOPE 205 study for the lenvatinib and everolimus combination and estimated from the respective Phase III clinical trials for axitinib, cabozantinib and nivolumab. Eisai believe that this best reflects the clinical data and the impact that relevant adverse events have on health-related quality of life. These estimations are summarised below and further detail can be found on page 166 of the company submission. Eisai estimated the total utility decrements separately for each relevant treatment, by assigning a utility decrement for grade 3 or higher adverse events based on the literature then estimating an average utility decrement for each treatment weighted by the proportion of patients who had each adverse event. The proportion of patients who had each adverse event was taken directly from each treatment's respective clinical trial. The derived utility decrement per treatment is as follows: • lenvatinib plus everolimus: -0.097 • axitinib: -0.072 • cabozantinib: -0.084 • nivolumab: -0.008 The total utility decrements were then calculated by applying the average duration of each adverse event. This was done by first dividing the median duration of each adverse event (based on HOPE 205 clinical trial patient-level data) by the duration of treatment(based on respective phase III clinical trials) to obtain the average proportion of time patients are treated for each AE, for each treatment: $Proportion\ of\ time\ treated\ for\ an\ AE = (median\ duration\ of\ AE) \div (median\ treatment\ duration)$ The resultant total utility decrements are as per those reported in the ACD ie: • lenvatinib plus everolimus: -0.0013 • axitinib: -0.010 • cabozantinib: -0.011 • nivolumab: -0.002 Although, as stated above, Eisai believe that the above utility decrements best reflect the clinical data and the impact that relevant adverse events have on health-related quality of life, the company has conducted a conservative scenario using the ERG-preferred base case model excluding the average duration of each adverse event ie using the utility decrements listed on the previous page.	event, and that many stopped treatment because of these adverse events. Please see section 3.21 of the FAD.

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			The revised base-case ICERs using the list prices are as follows: LEN+EVE versus axitinib: £59,489 LEN+EVE versus cabozantinib: Dominated LEN+EVE versus nivolumab: Dominated As stated previously, Eisai are in the very early stages of considering a large prospective study to capture further information around safety and quality of life with the aim to have results by 2020. Eisai would like NICE to consider whether this type of study would be sufficient to address the uncertainties around quality of life to gain a recommendation to go into the Cancer Drugs Fund.	
6		Eisai Limited	**Eisai have received approval for a revised PAS discount.** Eisai have revised the PAS discount as part of this ACD consultation and a completed PAS template with details of the revised PAS has been provided separately.	Comment noted. The committee considered the cost-effectiveness estimates including the revised PAS.
7		Eisai Limited	**Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS.** Eisai are disappointed that NICE has not recognised the benefits that the combination of lenvatinib and everolimus will bring to patients in England and Wales. Eisai believe that it is important that both clinicians and patients have access to this combination as it increases the choice of treatments available to them in the second-line setting. Although a number of single agents, including an anti-PD-1 inhibitor, have recently been recommended by NICE for use in this RCC patient population, these agents will not be suitable for all patients. There is still an unmet need, particularly for those patients with good functional state (ECOG performance status of 0-1) who are symptomatic with aggressive tumours (ie those with a high tumour growth rate).These patients need a rapid and high response and in such patients the expected combined efficacy of lenvatinib and everolimus would be a valid treatment option with a side effect profile that can be managed with dose modifications, interruptions or prompt medical treatment.	Thank you for your comment. The committee concluded that it could recommend lenvatinib plus everolimus, but only for people with an ECOG performance status score of 0 or 1. Please see section 3.24 of the FAD.
8		Ipsen	We agree that the utility decrements applied by the manufacturer seem implausible. In particular, the magnitude of decrement applied to axitinib and cabozantinib is more than three times that for everolimus, resulting in utility values which are not supported by the existing guidance documents for these medicines (TA333, TA463 and TA432). Further, the appraisal of nivolumab (S4.19, TA417) used the same utility values for axitinib and everolimus, accepting the views of the Clinical Experts that "health-related quality of life was similar for people whose condition was being treated	Thank you for your comment. The committee appreciated that uncertainty in the cost-effectiveness estimates came from the modelling assumptions about the impact of adverse

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			with these drugs". The Committee is noted as having “concerns” over the ERG’s base-case and we echo these. In the appraisals for everolimus (TA432), nivolumab (TA417) and cabozantinib (TA463), each of these drugs was more cost-effective than axitinib. We accept that the network meta-analysis for this appraisal incorporates the studies used in previous appraisals. However, the results are contradictory: axitinib now extendedly dominates cabozantinib. This supports the concern that the evidence base underpinning this appraisal is not robust.	events on health-related quality of life. The committee also considered the value patients and clinicians place on having treatment options. However, it concluded that lenvatinib plus everolimus could be recommended, but only for people with an ECOG performance status score of 0 or 1. Please see sections 3.21 and 3.24 of the FAD.
9		Kidney Cancer Support Network	The lenvatinib/everolimus combination has been designated a breakthrough therapy by the FDA as a treatment for advanced or metastatic RCC. As a breakthrough therapy, the lenvatinib/everolimus combination has been fast tracked for approval in a number of countries, including the US and Europe, based on the phase 3 clinical trial data.	Comment noted.
10		Kidney Cancer Support Network	Lenvatinib is a multiple kinase inhibitor against VEGF kinases, in addition to other tyrosine kinases implicated in pathogenic angiogenesis, tumour growth and cancer progression. It is the first multiple kinase inhibitor to gain marketing authorisation in North America and Europe for advanced RCC, and has proven to be effective in the treatment of certain kinds of thyroid cancer. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.	Comment noted. Lenvatinib plus everolimus is now recommended for advanced renal cell carcinoma in adults who have had 1 previous vascular endothelial growth factor (VEGF)-targeted therapy if their Eastern Cooperative Oncology Group (ECOG) performance status score is 0 or 1. Please see section 1.1 of the FAD.
11		Kidney Cancer Support Network	The lenvatinib/everolimus combination is the second drug combination for the treatment of mRCC to undergo NICE appraisal (the first being the bevacizumab/interferon combination). Previous drug combinations have proven to be unsuccessful as a result of unacceptable side effects. However, the lenvatinib/everolimus combination seems to be well tolerated, as well as proven to be more effective at extending overall survival compared to single agent therapy with lenvatinib and everolimus.	Thank you for your comment. The committee concluded that lenvatinib plus everolimus has a high burden of adverse events and is not well tolerated, even by patients who are relatively fit compared with the average person who would have this treatment in clinical practice. The committee also concluded that the evidence that lenvatinib extends overall survival is

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				statistically weak. Please see sections 3.9 and 3.13 of the FAD.
12		Kidney Cancer Support Network	Clinical trials have been conducted in previously treated advanced/metastatic RCC patients with the lenvatinib/everolimus combination in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug combination. If the government and the pharmaceutical industry cannot agree a price that allows the use of lenvatinib/everolimus on the NHS, we question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.	Comment noted. The committee makes decisions based on the clinical and cost-effectiveness evidence available for the technology.
13		Kidney Cancer Support Network	There are no biomarkers of response to treatment with current NHS treatments, and clinicians are unable to predict which patients will respond to which drug. This results in patients being unnecessarily exposed to the side effects of current treatments without the benefits of the drug if they are found to be non-responders. Selection of the most effective treatment for individual patients is accomplished by trial-and-error.	Comment noted.
14		Kidney Cancer Support Network	Current treatments have proven to shrink tumours and delay disease progression in some patients; however, current second-line treatment options are not effective for everyone. Choice in the second-line, and access to new innovative treatments remains paramount to managing the progression of this disease. Undue restrictions in accessing the lenvatinib/everolimus combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Having a choice in the second-line (and beyond) would enable patients and oncologists to better control this disease and individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.	Comment noted. Lenvatinib plus everolimus is now recommended for advanced renal cell carcinoma in adults who have had 1 previous vascular endothelial growth factor (VEGF)-targeted therapy if their Eastern Cooperative Oncology Group (ECOG) performance status score is 0 or 1. Please see section 1.1 of the FAD.
15		Kidney Cancer Support Network	Current treatments do not cure mRCC: the disease can be controlled for, on average, 2 years with current first-line treatments, after which second-line treatments can extend life for another year or more. Patients (and oncologists) need more choice in the second-line to effectively manage their disease and give them good quality life.	Comment noted. Lenvatinib plus everolimus is now recommended for advanced renal cell carcinoma in adults who have had 1 previous vascular endothelial growth factor (VEGF)-targeted therapy if their Eastern Cooperative Oncology Group (ECOG) performance status

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16		Kidney Cancer Support Network	A number of drug combinations have been shown to be effective in the treatment of non-clear cell RCC, especially papillary RCC. If recommended, the lenvatinib/everolimus combination could, therefore, be used to address an area of significant unmet need in the treatment of non-clear cell RCC.	Comment noted. Lenvatinib plus everolimus is now recommended for advanced renal cell carcinoma in adults who have had 1 previous vascular endothelial growth factor (VEGF)-targeted therapy if their Eastern Cooperative Oncology Group (ECOG) performance status score is 0 or 1. Please see section 1.1 of the FAD.

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NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 4 September 2017 please upload to NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[**Eisai Limited**]
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	[**N/A**]
Name of commentator person completing form:	[redacted]

Comment	**Comments**

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Eisai do not agree that the summary of the clinical evidence from the HOPE 205 study is a reasonable interpretation of the evidence for the reasons cited below:	
1	**Eisai does not agree that the design and size of the HOPE 205 trial precludes its results from forming a robust basis for decision-making.** This study was not pre-planned as a pivotal trial, but the results were so compelling that Eisai met with the regulators to discuss the possibility of this study supporting a marketing authorisation. The results of the study were also considered by the Committee for Medicinal Products for Human Use (CHMP) to be of major interest to the European Community on grounds of public health and therapeutic innovation, warranting their submission via the accelerated assessment procedure. The CHMP subsequently opted to grant a full marketing authorisation for the combination rather than a conditional approval requiring a post-approval efficacy study. No post-approval measures regarding evaluation of efficacy were required to be included in the risk management plan. From this, it should be understood that the European body tasked with the evaluation of benefit/risk of therapeutic agents intended for marketing in the EU (the CHMP), has concluded after an extensive review of the data over a 7-month period that the risk/benefit ratio of the combination is conclusive. Data from Study 205 show that lenvatinib in combination with everolimus was highly active in terms of progression free survival (PFS) and objective response rate (ORR) in patients with metastatic renal cell carcinoma (RCC). It is important to note that the PFS results by investigator assessment were corroborated by retrospective blinded independent assessment. In addition, there was a trend towards improved overall survival (OS) which was maintained in two additional OS analyses. Although a number of single agents, including an anti-PD-1 inhibitor, have recently been recommended by NICE for use in this RCC patient population, these agents will not be suitable for all patients. There is still an unmet need, particularly for those patients who are symptomatic with aggressive tumours who would benefit from a combination regimen for a rapid and high response. Given that the lenvatinib and everolimus combination is currently cost effective versus these agents, Eisai believe that it should be given “conditional approval” for entry into the Cancer Drugs Fund to allow for the opportunity for additional data to be collected to confirm the efficacy demonstrated in the HOPE 205 study. We are keen to work with NICE to address any uncertainties they believe exist with the currently available data in respect to relative treatment effectiveness and duration of treatment. The company does not currently have any ongoing studies in this second-line indication. However, Eisai are in the very early stages of considering a large prospective study to capture further information around safety and quality of life with the aim to have results by 2020. It would be possible to include efficacy outcome measures in this trial and Eisai would like NICE to consider whether this type of study would be sufficient to address the relevant uncertainties to gain a recommendation to go into the Cancer Drugs Fund.
2	**Eisai disagree that there is uncertainty around the optimal dose of lenvatinib.** Eisai acknowledges that dose modifications occurred during the HOPE 205 study with a median daily dose of 13.6 mg. Eisai does not believe that this represents an uncertainty around the

	optimal dose. Dose modification and interruption guidelines are available in the Summary of Product Characteristics (SPCs) of the other tyrosine kinase inhibitors (TKIs) used in advanced RCC. This represents the general approach when using these medicines in RCC ie using the recommended dose to induce tumour regression and then modifying or interrupting the dose to manage the tolerability for the patient, thereby maximising the overall time on treatment. This flexible dosing approach tailors the dose to the needs of the patient rather than indicating an uncertainty around the optimal dose. As stated in section 3.6 of the ACD, Eisai are conducting a clinical trial comparing the effects of a lower starting dose of 14mg of lenvatinib with the current recommended dose of 18mg. However, the objective of this study is to explore whether it is possible to achieve the same efficacy with a slight improvement in tolerability. The company thinks this is unlikely but is studying this in order to provide further information on benefit/risk of differing starting doses.
	Eisai do not agree that the differences in baseline characteristics between treatment groups in the HOPE 205 study impact the outcome of the study. It is important to note that the CHMP assessed that the imbalances in baseline characteristics between treatment groups were not of sufficient magnitude to impact the outcome of the HOPE 205 study. *Tumour burden* With respect to the differences in baseline characteristics related to tumour burden, as part of a response to the EMA during the regulatory process, Eisai conducted analyses using baseline tumour burden (number and site of metastases) as a potential confounding factor for both PFS and OS. Results of these analyses are consistent with the original ITT analyses, indicating that baseline tumor burden had no meaningful impact on the PFS and OS results and any observed imbalance did not impact the interpretation of the primary results. These results were accepted by the CHMP. <u>Progression-free survival</u> When the number of baseline metastases (0,1,2 or ≥3) was added to the analysis of investigator assessed PFS as a covariate in the Cox regression model (data cutoff date of 13 June 2014), the estimated HR and 95% confidence interval (CI) for the combination arm compared with the everolimus arm (HR=0.426 [95% CI: 0.252, 0.720]) from the model was consistent with that of the original ITT analysis (HR=0.401 [95% CI: 0.239, 0.675]). Similarly, the HRs and CIs for the PFS subgroup analysis between the combination and everolimus arms by site of metastasis were all consistent with that for the overall population, and favoured the combination arm across all subgroups. These results demonstrate that the status of and the imbalance in baseline metastases had no meaningful impact on the overall conclusion for the PFS result. <u>Overall survival</u> Similar to the results for PFS, when the number of baseline metastases was included as an additional covariate in the analysis of OS using the Cox regression model (data cutoff date of 31 July 2015), the estimated HR and 95% confidence interval (CI) for the combination arm compared with the everolimus arm (HR=0.641 [95% CI: 0.389, 1.056]) from the model were consistent with that of the original ITT analysis (HR=0.588 [95% CI: 0.359, 0.965]). In addition, the HRs and CIs for the combination arm compared with the everolimus arm by site of metastasis were all consistent with that for the overall population, and favoured the combination arm across all subgroups.

	Previous therapy With respect to differences in baseline characteristics related to previous treatment, post-hoc subgroup analyses conducted as part of EMA responses during the regulatory process have shown that the combination arm demonstrated superior efficacy compared with everolimus in Study 205, regardless of duration of prior anti-VEGF therapy received. These results suggest that prior anti-VEGF therapy had no meaningful impact on the overall conclusion for PFS and OS results and support the opinion of the clinical expert that it is debatable that length of prior treatment is a prognostic factor. Progression-free survival When the duration of treatment with prior VEGF-targeted therapy was added to the analysis of investigator assessed PFS as a covariate in the Cox regression model (data cutoff date of 13 June 2014), the estimated HR and CI for the combination arm compared with the everolimus arm (HR=0.433 [95% CI: 0.252, 0.742]) from the model was consistent with that of the original ITT analysis (HR=0.401 [95% CI: 0.239, 0.675]). Overall survival Similar to the results for PFS, when the duration of treatment with prior VEGF-targeted therapy was included as an additional covariate in the analysis of OS using the Cox regression model (data cutoff date of 31 July 2015), the estimated HR and 95% confidence interval (CI) for the combination arm compared with the everolimus arm (HR=0.630 [95% CI: 0.381, 1.040]) from the model were consistent with that of the original ITT analysis (HR=0.588 [95% CI: 0.359, 0.965]). The results for PFS, OS and objective response rate (ORR) in the HOPE 205 study favoured the combination arm over the everolimus monotherapy arm regardless of which prior VEGF-targeted therapy was used. An ad hoc subgroup analysis by prior type of treatment showed that results favoured the combination arm over everolimus regardless of which prior VEGF-targeted therapy was used, with nearly identical HRs for investigator assessed PFS (data cutoff date of 13 June 2014) in both subgroup categories (sunitinib, HR=0.356; other VEGF-targeted therapies, HR=0.350; *P*=0.003 and *P*=0.017 for the 2 subgroups, respectively). The HRs for OS for the sunitinib and other-VEGF subgroups were 0.532 and 0.639, respectively, and favoured the combination over everolimus. Similar results were seen for ORR by prior therapy ie in patients who received prior sunitinib, the ORR was 41.7% for the combination arm versus 3.6% versus the everolimus arm and for those who received different prior VEGF-targeted therapy, the ORR again favoured the combination arm (46.7%) compared with 9.1% for everolimus. It is also important to note that a separate Phase III trial of sunitinib versus pazopanib in the first-line treatment of advanced RCC showed similar efficacy between these 2 agents, with a median PFS of 8.4 months for pazopanib (95% confidence interval [CI], 8.3 to 10.9) and 9.5 months for sunitinib (95% CI, 8.3 to 11.1) and an HR of 1.05 (1). This trial demonstrates that there is little difference in efficacy among anti-VEGF TKI agents in the first-line setting. Therefore, it is highly unlikely that a particular first-line anti-VEGF agent would have a differential effect on efficacy once a patient enters the second-line setting. **Reference:** 1. Motzer RJ, Hutson TE, Cella D, et al. Pazopanib versus sunitinib in metastatic renal-cell carcinoma. NEJM 2013;369: 722-731
4	**The lenvatinib plus everolimus combination has a manageable safety profile.** It is important to note that, as stated on the slides presented at the first NICE committee meeting, patient and professional feedback obtained during this NICE STA to date has noted that this

	combination does have more side effects than the individual treatments, but that these were considered manageable. Despite the availability of single agents in this setting, there is still an unmet need, particularly for those patients who are symptomatic with aggressive tumours (ie those with a high tumour growth rate).These patients need a rapid and high response and the rationale behind the combination was to start on the recommended dose to induce optimal tumour regression followed by individual adjustments to manage tolerability. This flexible dosing approach tailors the dose to the needs of the patient and maximises the time on treatment. Safety analyses of the HOPE 205 study have showed that lenvatinib as a combination therapy, has a predictable and manageable safety profile. In general, the overall adverse event (AE) profile for combination lenvatinib/everolimus was as expected for these classes of compounds and was consistent with the safety profiles of lenvatinib and everolimus as monotherapy. Based on an initial analysis of the AEs that were observed, Eisai considers there to be 4 potential worsening safety signals for combination therapy compared with either or both monotherapy agents: diarrhoea, hypercholesterolemia, hypothyroidism, and increased blood TSH. All of these can be managed with adequate monitoring, dose reduction and interruption, and prompt medical treatment.
Eisai do not agree that the summary of the cost effectiveness evidence is a reasonable interpretation of the evidence for the reasons cited below:	
1	**The utility values used in the model do reflect the quality of life appropriately.** The wording currently in the ACD does not fully reflect the methodology used by Eisai in the company submission to estimate the impact of adverse events on health-related quality of life. It is important to note that the company's estimations incorporate the average duration of each adverse event, taken directly from the HOPE 205 study for the lenvatinib and everolimus combination and estimated from the respective Phase III clinical trials for axitinib, cabozantinib and nivolumab. Eisai believe that this best reflects the clinical data and the impact that relevant adverse events have on health-related quality of life. These estimations are summarised below and further detail can be found on page 166 of the company submission. Eisai estimated the total utility decrements separately for each relevant treatment, by assigning a utility decrement for grade 3 or higher adverse events based on the literature then estimating an average utility decrement for each treatment weighted by the proportion of patients who had each adverse event. The proportion of patients who had each adverse event was taken directly from each treatment's respective clinical trial. The derived utility decrement per treatment is as follows: • lenvatinib plus everolimus: -0.097 • axitinib: -0.072 • cabozantinib: -0.084 • nivolumab: -0.008 The total utility decrements were then calculated by applying the average duration of each adverse event. This was done by first dividing the median duration of each adverse event (based on HOPE 205 clinical trial patient-level data) by the duration of treatment(based on respective phase III clinical trials) to obtain the average proportion of time patients are treated for each AE, for each treatment: $Proportion\ of\ time\ treated\ for\ an\ AE = (median\ duration\ of\ AE) \div (median\ treatment\ duration)$

	The resultant total utility decrements are as per those reported in the ACD ie: • lenvatinib plus everolimus: -0.0013 • axitinib: -0.010 • cabozantinib: -0.011 • nivolumab: -0.002 Although, as stated above, Eisai believe that the above utility decrements best reflect the clinical data and the impact that relevant adverse events have on health-related quality of life, the company has conducted a conservative scenario using the ERG-preferred base case model excluding the average duration of each adverse event ie using the utility decrements listed on the previous page. The revised base-case ICERs using the list prices are as follows: LEN+EVE versus axitinib: £59,489 LEN+EVE versus cabozantinib: Dominated LEN+EVE versus nivolumab: Dominated As stated previously, Eisai are in the very early stages of considering a large prospective study to capture further information around safety and quality of life with the aim to have results by 2020. Eisai would like NICE to consider whether this type of study would be sufficient to address the uncertainties around quality of life to gain a recommendation to go into the Cancer Drugs Fund.
3	**Eisai have received approval for a revised PAS discount.** Eisai have revised the PAS discount as part of this ACD consultation and a completed PAS template with details of the revised PAS has been provided separately.

Overall Eisai does not believe that these provisional recommendations provide sound and suitable guidance to the NHS.

Eisai are disappointed that NICE has not recognised the benefits that the combination of lenvatinib and everolimus will bring to patients in England and Wales.

Eisai believe that it is important that both clinicians and patients have access to this combination as it increases the choice of treatments available to them in the second-line setting. Although a number of single agents, including an anti-PD-1 inhibitor, have recently been recommended by NICE for use in this RCC patient population, these agents will not be suitable for all patients.

There is still an unmet need, particularly for those patients with good functional state (ECOG performance status of 0-1) who are symptomatic with aggressive tumours (ie those with a high tumour growth rate).These patients need a rapid and high response and in such patients the expected combined efficacy of lenvatinib and everolimus would be a valid treatment option with a side effect profile that can be managed with dose modifications, interruptions or prompt medical treatment.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 5pm on 4 September 2017 please upload to NICE DOCS

- Do not paste other tables into this table – type directly into the table.
- Please underline all confidential information, and separately highlight information that is submitted under 'commercial in confidence' in turquoise and all information submitted under 'academic in confidence' in yellow. If confidential information is submitted, please also send a 2nd version of your comment with that information replaced with the following text: 'academic / commercial in confidence information removed'. See the Guide to the processes of technology appraisal (section 3.1.23 to 3.1.29) for more information.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the appraisal consultation document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations 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 comments we received, and are not endorsed by NICE, its officers or advisory committees.

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 4 September 2017 please upload to NICE DOCS

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Kidney Cancer Support Network
Disclosure Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	[redacted]
Comment	**Comments**

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

NICE National Institute for Health and Care Excellence

Consultation on the appraisal consultation document – deadline for comments 4 September 2017 please upload to NICE DOCS

number	Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	The lenvatinib/everolimus combination has been designated a breakthrough therapy by the FDA as a treatment for advanced or metastatic RCC. As a breakthrough therapy, the lenvatinib/everolimus combination has been fast tracked for approval in a number of countries, including the US and Europe, based on the phase 3 clinical trial data.
2	Lenvatinib is a multiple kinase inhibitor against VEGF kinases, in addition to other tyrosine kinases implicated in pathogenic angiogenesis, tumour growth and cancer progression. It is the first multiple kinase inhibitor to gain marketing authorisation in North America and Europe for advanced RCC, and has proven to be effective in the treatment of certain kinds of thyroid cancer. Currently, UK cancer survival rates trail about 10 years behind other comparable European countries, including Italy and Austria. If the UK is to improve patient outcomes, including patient experience as well as overall survival, it is vital that innovative new drugs with different modes of action are made available to patients in order that they have the best care possible. If these drugs are not made available, it leaves UK patients at a major disadvantage in terms of the availability of innovative cancer treatments; these patients are likely to die prematurely compared to the rest of Europe and North America.
3	The lenvatinib/everolimus combination is the second drug combination for the treatment of mRCC to undergo NICE appraisal (the first being the bevacizumab/interferon combination). Previous drug combinations have proven to be unsuccessful as a result of unacceptable side effects. However, the lenvatinib/everolimus combination seems to be well tolerated, as well as proven to be more effective at extending overall survival compared to single agent therapy with lenvatinib and everolimus.
4	Clinical trials have been conducted in previously treated advanced/metastatic RCC patients with the lenvatinib/everolimus combination in the UK. The patients who participated in these trials did so in the expectation that their data would enable other patients in the UK to benefit from this drug combination. If the government and the pharmaceutical industry cannot agree a price that allows the use of lenvatinib/everolimus on the NHS, we question whether patients will continue to support future research by taking part in clinical trials. Also, it is questionable whether patients and the public will continue to donate to charities, such as Cancer Research UK, to enable other patients to benefit from new, innovative and clinically effective drugs if the precedent for these drugs is rejection by NICE.
5	There are no biomarkers of response to treatment with current NHS treatments, and clinicians are unable to predict which patients will respond to which drug. This results in patients being unnecessarily exposed to the side effects of current treatments without the benefits of the drug if they are found to be non-responders. Selection of the most effective treatment for individual patients is accomplished by trial-and-error.
6	Current treatments have proven to shrink tumours and delay disease progression in some patients; however, current second-line treatment options are not effective for everyone. Choice in the second-line, and access to new innovative treatments remains paramount to managing the progression of this disease. Undue restrictions in accessing the lenvatinib/everolimus combination would simply add unnecessary additional burden to patients with a terminal diagnosis. Having a choice in the second-line (and beyond) would enable patients and oncologists to better control this disease and individualise treatment plans according to specific disease/treatment history and contraindications, thereby enabling the best possible quality of life for the patient.
7	Current treatments do not cure mRCC: the disease can be controlled for, on average, 2 years with current first-line treatments, after which second-line treatments can extend life for another year or

	more. Patients (and oncologists) need more choice in the second-line to effectively manage their disease and give them good quality life.
8	A number of drug combinations have been shown to be effective in the treatment of non-clear cell RCC, especially papillary RCC. If recommended, the lenvatinib/everolimus combination could, therefore, be used to address an area of significant unmet need in the treatment of non-clear cell RCC.

Insert extra rows as needed

Checklist for submitting comments

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- Complete the disclosure about links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into 1 response. We cannot accept more than 1 set of comments from each organisation.
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Comments on the ACD Received from the Public through the NICE Website

Name	Ipsen
Role	Pharmaceutical Industry
Location	England
Conflict	I work for the manufacturer of one of the comparators in this appraisal (cabozantinib, Ipsen)
Notes	

Comments on individual sections of the ACD:

We agree that the utility decrements applied by the manufacturer seem implausible. In particular, the magnitude of decrement applied to axitinib and cabozantinib is more than three times that for everolimus, resulting in utility values which are not supported by the existing guidance documents for these medicines (TA333, TA463 and TA432). Further, the appraisal of nivolumab (S4.19, TA417) used the same utility values for axitinib and everolimus, accepting the views of the Clinical Experts that "health-related quality of life was similar for people whose condition was being treated with these drugs".

The Committee is noted as having “concerns” over the ERG’s base-case and we echo these. In the appraisals for everolimus (TA432), nivolumab (TA417) and cabozantinib (TA463), each of these drugs was more cost-effective than axitinib. We accept that the network meta-analysis for this appraisal incorporates the studies used in previous appraisals. However, the results are contradictory: axitinib now extendedly dominates cabozantinib. This supports the concern that the evidence base underpinning this appraisal is not robust.

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

ERG critique of the company's response to the first Appraisal Consultation Document

This report was commissioned by the NIHR HTA Programme as project number 16/108/10

BMJ Technology Assessment Group

The company has provided comments on the Appraisal Consultation Document (ACD) resulting from the first Appraisal Committee Meeting (ACM) on 19 July 2017. This document summarises the Evidence Review Group's (ERG's) critique on the company's comments.

Trial design and sample size of HOPE 205

The trial HOPE 205, comparing lenvatinib in combination with everolimus, hereafter referred to as lenvatinib combination therapy, and everolimus monotherapy, provides the only direct evidence informing the efficacy and safety of lenvatinib combination therapy. HOPE 205 is a well conducted multicentre, open label, phase II trial, with around 50 patients in each treatment group. All outcomes in the trial were investigator assessed although the regulatory agencies, European Medicines Agency (EMA) and US Food and Drug Administration (FDA), requested *post-hoc* independent radiology review (IRR) of progression free survival (PFS) and response data.

As stated in the ERG report, the ERG considers the trial to be largely well conducted and the statistical analyses to be appropriate. However, the ERG is concerned about the small sample size of the study, which introduces substantial uncertainty around the observed efficacy and safety of lenvatinib combination therapy. In addition, the ERG is concerned about the open label design and the lack of blinded outcomes assessment of PFS and tumour response, which was only done retrospectively at the request of the EMA/FDA.

The company highlights that the Committee for Medicinal Products for Human Use (CHMP) granted a full marketing authorisation for the combination therapy rather than a conditional approval requiring a post-approval efficacy study, which, according to the company, should be understood as the EMA has concluded that the risk/benefit ratio of the combination is conclusive. The company also states that there is an unmet clinical need, particularly for patients who are symptomatic and have aggressive tumours, who would benefit from a combination regimen for a rapid and high response.

The ERG agrees with the company that the results from HOPE 205 clearly show a benefit of lenvatinib combination treatment compared with everolimus, however, due to the small size of the trial it was not powered to detect a statistically significant difference in overall survival (OS) and there is substantial uncertainty around the magnitude of the effect size in terms of PFS and response rate.

The ERG also notes that, it has not been shown that the lenvatinib combination regimen leads to a more rapid response than any of the relevant single agent comparators: nivolumab, cabozantinib, and axitinib. In HOPE 205, median time to response was similar in the lenvatinib combination and everolimus groups and corresponded with the first protocol-specified tumour assessment timepoint: 8.2 weeks and 8.0 weeks, respectively. Similarly, for nivolumab and cabozantinib, time to response was similar between

these treatments compared with everolimus in the CheckMate 025 and METEOR trials. The ERG also notes that although the objective response rate (ORR) was higher for the lenvatinib combination versus everolimus than for nivolumab or cabozantinib versus everolimus, there was no statistically significant difference in ORR in the company's indirect analysis of lenvatinib combination versus nivolumab or cabozantinib.

Dose of lenvatinib

In HOPE 205 patients randomised to lenvatinib combination therapy received lenvatinib 18mg/day plus everolimus 5mg/day. Dose reductions and dose interruptions done in accordance with prescribing information were allowed to manage toxicities of the study drugs and the median daily dose of lenvatinib was 13.6mg, 75% of the recommended daily dose. A large proportion of patients had dose interruptions (80.4%) or dose reduction (70.6%) of lenvatinib; the majority due to adverse events.

As stated by the company, dose modification and interruption represents the approach for managing adverse effects of lenvatinib and other tyrosine kinase inhibitors (TKIs) used in advanced renal cell carcinoma (RCC), with guidelines available in the Summary of Product Characteristics (SPCs) of each of these interventions. Using the recommended dose to induce tumour regression and then modifying or interrupting the dose to manage the tolerability for the patient, maximises the overall time on treatment.

The ERG agrees with the company that, the median daily dose does not in itself represent an uncertainty around the optimal dose. However, the FDA has concerns about the serious adverse events requiring dose reduction or interruption in HOPE 205, and has requested a clinical trial comparing the effects of a lower starting dose of 14mg of lenvatinib with the current recommended dose of 18mg.[1] As stated by the company, the objective of this trial is to explore whether it is possible to achieve the same efficacy with 14mg as with 18mg, but with a slight improvement in tolerability. This trial may confirm the optimal dose in terms of the efficacy and tolerability of lenvatinib combination therapy.

Differences in baseline characteristics between treatment groups

The patients' baseline characteristics in HOPE 205 were relatively well balanced between the trial arms. However, as noted in the ERG report, some differences potentially indicate a poorer prognosis for the everolimus group compared with patients randomised to lenvatinib combination therapy. In the everolimus group there was a larger proportion of patients with more than one metastasis, resulting in slightly more patients having bone, liver, lung and lymph node metastases compared with the lenvatinib combination group. Bone and liver metastases are associated with a poorer prognosis than metastases in other locations. Patients in the everolimus monotherapy group also had a slightly shorter duration of

prior VEGF-targeted therapy and fewer patients with complete or partial response to first-line VEGF-targeted therapy compared with patients in the lenvatinib combination group. Although the differences between the trial arms are based on very small numbers of patients, and likely to be due to chance, they are consistent with a potentially worse prognosis for the patients in the everolimus group compared with patients randomised to lenvatinib combination therapy.

The company does not agree that the differences in baseline characteristics between treatment groups in HOPE 205 impact the outcomes of the study. The company notes that, the CHMP assessed that the imbalances in baseline characteristics between treatment groups were not of sufficient magnitude to impact the outcome of the HOPE 205 study. The company goes on to present ITT data compared with data adjusted for tumour burden and previous therapy (Table 1): the company conducted these analyses, using baseline tumour burden (number and site of metastases) and duration of prior therapy as potential confounding factors for both PFS and OS, as part of a response to the EMA during the regulatory process.

Table 1. PFS and OS adjusted for imbalances in baseline characteristics

	PFS **HR (95% CI)**	**OS** **HR (95% CI)**
ITT	0.401 (0.239 to 0.675)	0.588 (0.359 to 0.965)
Adjusted for number of baseline metastases (0,1,2 or ≥3)	0.426 (0.252 to 0.720)	0.641 (0.389 to 1.056)
Adjusted for duration prior VEGF-targeted therapy	0.433 (0.252 to 0.742)	0.630 (0.381 to 1.040)
Abbreviations:		

The ERG agrees with the company that the adjusted and ITT analysis are consistent in terms of direction of effect (for PFS and OS), and statistical significance (for PFS only) for both number of baseline metastases and duration of previous therapy. Although the change in the point estimate between the adjusted and ITT estimate is relatively small for both number of baseline metastases and duration of previous therapy, the difference between the treatment groups consistently decreases when the difference in baseline characteristic has been adjusted for. Also, the ERG notes that there were other imbalances in the baseline characteristics (type of metastases and proportion of patients with complete or partial response to prior therapy) that all indicate a worse prognosis for the comparator group (everolimus) compared to the lenvatinib combination group. According to the company, the HRs and CIs for the PFS subgroup analysis between the combination and everolimus arms by site of metastasis were all consistent with that for the overall population, and favoured the combination arm across all subgroups, but the company did not present the numbers for these analyses in their comments to the ACD.

It is unclear how big an impact these differences will have on the point estimates for PFS and OS when taken together, but the potential impact of these differences would likely lead to an overestimate of the lenvatinib combination therapy compared with everolimus monotherapy. However, the ERG reiterates that, the number of patients are very small and the potential impact of the differences should be interpreted with caution.

Safety profile

The company acknowledges that treatment with lenvatinib combination therapy leads to more side effects than everolimus monotherapy: grade 3 or higher treatment-emergent and treatment-related adverse events (AEs) were more frequent in the combination group (72.5% and 64.7% respectively) than the everolimus group (54.0% and 42.0% respectively), and as expected most adverse events leading to treatment adjustments were related to the study treatments.

The company states that, the safety analyses of the HOPE 205 trial have showed that lenvatinib, as a combination therapy, has a predictable and manageable safety profile; treatment related AEs can be managed with adequate monitoring, dose reduction and interruption, and prompt medical treatment. The company also notes that, these adverse events were considered manageable according to patient and professional feedback obtained during this NICE STA. Although, the clinical expert at the first ACM considered that it would be difficult to offer a treatment that leads to grade 3 or 4 AEs in almost three-quarters of patients.

The ERG notes that, the impact of clinical benefit and side effects are considered in the cost-effectiveness analysis of this STA. However, if lenvatinib combination therapy were to be available as a therapy option for advanced RCC in the NHS, it would be up to individual clinicians and patients to decide if the side effect profile of lenvatinib combination therapy is acceptable and manageable.

The company again states that there is an unmet clinical need, particularly for patients who are symptomatic and have aggressive tumours, who would benefit from a combination regimen for a rapid and high response.

The ERG re-iterates that, it has not been shown that the lenvatinib combination regimen leads to a more rapid response than any of the relevant single agent comparators. The ERG also notes that, although the objective response rate (ORR) was higher for the lenvatinib combination versus everolimus than for nivolumab or cabozantinib versus everolimus, there was no statistically significant difference in ORR in the company's indirect comparison of lenvatinib combination versus nivolumab or cabozantinib. Similarly, there was [redacted] in the proportion of patients experiencing at

least one grade 3 or 4 AE between lenvatinib combination therapy and cabozantinib based on the company's indirect comparison [redacted], but a higher proportion of patients experienced at least one treatment-related grade 3 or 4 AE with lenvatinib combination therapy compared with nivolumab [redacted].

Utility values

The ACD outlines the committee's concerns regarding the utility decrements applied for adverse events, stating that they do not reflect the adverse event profile of lenvatinib combination due to the small magnitude of the decrements applied in the model. The committee also state that they do not correlate with the observation in the HOPE 205 trial that all patient receiving lenvatinib combination therapy experienced an adverse event, causing many patients to withdraw from treatment.

In response to the committee's comments in the ACD regarding the appropriateness of the utility decrements applied for adverse events, the company reiterated that the decrements incorporate an adjustment for the duration of effect of the adverse events, as well as accounting for the proportion of patients who experienced the events. These two adjustments effectively give the average impact of adverse events per person per cycle, and this perhaps caused the committee's concerns that the impact appeared to be minimal. The ERG considers the approach taken by the company to be reasonable, although would have preferred to have had the decrements, without a duration adjustment, applied for only the duration that patients experienced the adverse events in the respective trials. However, the difference in these two approaches is not expected to make an important difference to the model results.

The ERG considers that the adverse events in the model correlate with those observed in the HOPE 205 trial, as the prevalence and duration data used to weight the utility decrements are taken directly from the HOPE 205 trial. Also, the treatment withdrawal relating to severe adverse events allows patients to recover from the adverse events, hence, experiencing the reduced quality of life for a shorter duration. This will be captured in the duration adjustment, and supports the company's approach for applying this adjustment. The treatment duration and treatment effects also inherently capture the impact of treatment withdrawal relating to this intolerable toxicity.

To account for the committee's concerns, the company chose to provide the results of a conservative scenario analysis, whereby the duration adjustment is removed. This effectively implies that the duration of adverse events is equivalent to the duration of treatment. The resulting incremental cost-effectiveness ratio (ICER) based on list prices was £59,489 per quality-adjusted life-year (QALY)

compared to axitinib. Cabozantinib and nivolumab were both dominated. The ERG has produced these incremental results in full in Table 2 and

Table 3, based on the list prices for all drugs, and based on the company's revised patient access scheme (PAS) discount of [redacted], respectively.

Table 2. Company's alternative utility decrement using ERG base case (list prices)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
Axitinib	43,473	1.85	1.14	-	-	-	-
Lenvatinib combination	74,318	2.69	1.66	30,845	0.83	0.52	59,489
Cabozantinib	94,174	2.36	1.44	19,856	-0.33	-0.22	Dominated
Nivolumab	106,063	2.20	1.40	31,745	-0.48	-0.26	Dominated

Table 3. Company's alternative utility decrement using ERG base case (PAS for lenvatinib only)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Revised Patient Access Scheme

The company submitted a revised simple PAS discount of [redacted], increased from the initial PAS discount of [redacted]. The results of the ERG base case (outlined in the ACD as the committee's preferred analysis) using this revised PAS for lenvatinib, and list prices for the comparators, are given in Table 4. This analysis differs from the scenario given above only by having the duration adjustment applied to the adverse event utility decrements. For comparison, the ERG base case ICER for lenvatinib combination compared with axitinib, using the PAS discount of [redacted], was [redacted].

Table 4. ERG preferred base case (revised lenvatinib PAS applied)

Treatment	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

The results of the analyses presented in this document using the comparator PASs as well as the lenvatinib PAS are provided in a confidential appendix.

References

1. Food and Drug Administration (FDA). SUPPLEMENT APPROVAL LETTER, LENVIMA2016. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2016/206947Orig1s003ltr.pdf.