NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Appraisal consultation document

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

The Department of Health has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using lenvatinib plus everolimus in the NHS in England. The appraisal committee has considered the evidence submitted by the company and the views of non-company consultees and commentators, clinical experts and patient experts.

This document has been prepared for consultation with the consultees. It summarises the evidence and views that have been considered, and sets out the recommendations made by the committee. NICE invites comments from the consultees and commentators for this appraisal and the public. This document should be read along with the evidence (see the committee papers).

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 recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of race, gender, disability, religion or belief, sexual orientation, age, gender reassignment, pregnancy and maternity?

Issue date: August 2017

Note that this document is not NICE's final guidance on this technology. The recommendations in section 1 may change after consultation.

After consultation:

- The appraisal committee will meet again to consider the evidence, this appraisal consultation document and comments from the consultees.
- At that meeting, the committee will also consider comments made by people who are not consultees.
- After considering these comments, the committee will prepare the final appraisal determination.
- Subject to any appeal by consultees, the final appraisal determination may be used as the basis for NICE's guidance on using lenvatinib plus everolimus in the NHS in England.

For further details, see NICE's guide to the processes of technology appraisal.

The key dates for this appraisal are:

Closing date for comments: 04 September 2017

Second appraisal committee meeting: 20 September 2017

Details of membership of the appraisal committee are given in section 5.

1 Recommendations

1.1 Lenvatinib plus everolimus is not recommended, within its marketing authorisation, for treating advanced renal cell carcinoma in adults who have had 1 previous vascular endothelial growth factor (VEGF)-targeted therapy.

1.2 This recommendation is not intended to affect treatment with lenvatinib plus everolimus that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop.

Why the committee made these recommendations

Clinical trial evidence suggests that lenvatinib plus everolimus increases the length of time people live by 10.1 months compared with everolimus alone. But the main trial included a small number of patients, which makes the results unreliable and the differences between groups unclear. More people who had lenvatinib plus everolimus had serious side effects, leading to dose interruptions, than those who had everolimus alone.

Lenvatinib plus everolimus did not meet NICE's criteria for a life-extending treatment at the end of life. The cost-effectiveness estimate for lenvatinib plus everolimus varied because of uncertainties in the clinical evidence and the economic modelling. The cost-effectiveness estimates compared with all comparators were much more than what NICE normally considers acceptable (that is, £30,000 per quality-adjusted life year gained). Given the high cost-effectiveness estimates and the substantial uncertainty in the results, lenvatinib plus everolimus cannot be recommended.

2 The technology

Lenvatinib (Kisplyx, Eisai)	
Marketing authorisation	Lenvatinib is indicated 'in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma following 1 prior vascular endothelial growth factor (VEGF)-targeted therapy'.
Recommended dose and schedule	The recommended daily dose of lenvatinib is 18 mg (1×10 mg capsule and 2×4 mg capsules) once daily, with 5 mg of everolimus once daily.
Price	The list price of lenvatinib is £1,437.00 per 30-capsule pack (4 mg and 10 mg). The list price of everolimus is £2,250.00 per 30-tablet pack of 5 mg everolimus. The company has agreed a patient access scheme with the Department of Health. If lenvatinib had been recommended, this scheme would provide a simple discount to the list price of lenvatinib with the discount applied at the point of purchase or invoice. The level of the discount is commercial in confidence. The Department of Health considered that this patient access scheme would not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (section 5) considered evidence submitted by Eisai and a review of this submission by the evidence review group (ERG). See the committee papers for full details of the evidence.

Current NHS treatments

Up to 4 lines of treatment are available in the NHS for advanced renal cell carcinoma

3.1 In the NHS most people with newly diagnosed advanced renal cell carcinoma will first be offered 1 of 2 tyrosine kinase inhibitor (TKI); pazopanib or sunitinib, as recommended in NICE technology appraisal guidance. If the cancer progresses and people are fit enough to have further treatment, most are then offered axitinib (also a TKI), nivolumab (a programmed cell death protein 1 [PD-1] inhibitor), or everolimus (a mammalian target of rapamycin [mTOR] inhibitor), as recommended in

NICE technology appraisal guidance. Final draft guidance on cabozantinib (a TKI) recommends it for advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF)-targeted therapy (which includes pazopanib and sunitinib). If the cancer progresses again, people may have, as third-line treatment, whichever of axitinib, nivolumab, everolimus or cabozantinib was not used as second-line treatment. The committee recalled its previous discussion in the appraisal of cabozantinib that the use of everolimus was likely to shift to later in the treatment pathway so that everolimus was predominantly used in clinical practice after 3 previous treatments, that is, as a fourth-line treatment. It concluded that the current treatment pathway offered options for NHS patients.

Place in the treatment pathway

Lenvatinib plus everolimus is a second-line treatment

3.2 According to the marketing authorisation, lenvatinib plus everolimus is indicated for advanced renal cell carcinoma after 1 previous VEGF-targeted therapy. The clinical effectiveness evidence on lenvatinib plus everolimus was limited to second-line use, that is, all patients included in the main clinical trial had had only 1 previous treatment. The clinical expert explained that in clinical practice, lenvatinib plus everolimus would not be expected to be used after more than 1 previous treatment given the absence of evidence beyond second-line treatment. The committee concluded that it would appraise lenvatinib plus everolimus for people who have had only 1 previous VEGF-targeted therapy, that is, as a second-line treatment.

Comparators

Axitinib, nivolumab and cabozantinib are the relevant comparators

3.3 The committee recalled that at the point at which lenvatinib plus everolimus would be used (that is, after 1 previous treatment), axitinib, nivolumab, and cabozantinib are also treatment options. Everolimus is

likely to be used later as a fourth-line treatment (see section 3.1). The committee noted that the final scope also included best supportive care as a comparator, although the company and the ERG did not consider it to be a relevant alternative to lenvatinib plus everolimus in clinical practice. The committee agreed that best supportive care may be suitable for a small group of people who are not fit enough to have active treatment, but it considered that this group was also unlikely to be offered lenvatinib plus everolimus. Also, the committee understood that after positive NICE recommendation guidance on nivolumab and cabozantinib, there were even fewer people for whom no active therapy was appropriate, and they were unlikely to reflect those who would be offered lenvatinib plus everolimus. The committee concluded that the relevant comparators for lenvatinib plus everolimus were axitinib, nivolumab and cabozantinib.

Clinical trial evidence

HOPE 205 is an open-label, randomised controlled trial

3.4 The main clinical evidence for lenvatinib plus everolimus came from HOPE 205, an open-label phase II randomised controlled trial comparing 3 treatments: lenvatinib plus everolimus (n=51), lenvatinib alone (n=52), and everolimus alone (n=50). The committee agreed that it would focus on the comparison of lenvatinib plus everolimus with everolimus alone because lenvatinib alone was not licensed for advanced renal cell carcinoma. The primary outcome in the trial was investigator-assessed progression-free survival, with overall survival, tumour response and safety as secondary outcomes. Progression-free survival by independent review was assessed post hoc (that is, not planned in the study protocol) following a request from the regulators.

HOPE 205 is a small open-label trial with reduced power to detect differences

3.5 The committee discussed the following limitations of HOPE 205:

- As a phase II trial, HOPE 205 was designed so that 90 progression-free survival events were needed to detect a hazard ratio [HR] of 0.67 with 70% power using a 1-sided significance level of 0.15 for the comparison of lenvatinib plus everolimus with everolimus alone. The company explained that HOPE 205 was not designed to be a 'registration trial', but that it was submitted for regulatory approval because the reported results were thought to be compelling. The committee recognised that, because the trial had 70% power for a significance level of 0.15, the investigators were willing to accept a risk of false positive results of 15%.
- Because HOPE 205 was an open-label trial, both the patients and the investigators knew the allocated treatment. Also, unblinded investigators assessed the primary outcome progression-free survival. The committee recognised that the design of HOPE 205 was a source of bias.
- HOPE 205 included a small number of patients (around 100 patients across the lenvatinib plus everolimus and the everolimus alone groups). This introduced considerable uncertainty around the estimates of efficacy and safety of lenvatinib plus everolimus, and meant that the differences between the treatment groups were unclear.

The company stated that it has no further plans to collect comparative data on lenvatinib plus everolimus and other second-line treatments. The committee concluded that, given the design of the trial and small number of patients included, the results of HOPE 205 were unlikely to form a robust basis for decision-making.

Dose

There is uncertainty around the optimal dose of lenvatinib

3.6 In HOPE 205, the actual median daily dose of lenvatinib was 13.6 mg, only 75% of the approved daily dose of 18 mg in the marketing authorisation. Patients in the lenvatinib plus everolimus group reduced

their doses more than those in the everolimus alone group (by 65% compared with 14%). The clinical expert pointed out that the company has an ongoing trial comparing the recommended dose of lenvatinib (18 mg) with a lower dose (14 mg), which the expert took to suggest that there was uncertainty around the optimal dose of lenvatinib. The committee concluded that it can only appraise lenvatinib at its approved dose, but that the modelled dose should appropriately reflect HOPE 205 from which the estimates on the effectiveness and safety of lenvatinib plus everolimus were obtained.

Generalisability of trial results to the NHS

Patients in HOPE 205 reflect people who would be offered second-line treatment in the NHS

3.7 The committee discussed whether patients in HOPE 205 reflected patients in the NHS, noting that 11 of the 37 study sites were in the UK. In particular, it reflected on patient characteristics at baseline:

- Most patients had had either sunitinib (63%) or pazopanib (22%) as their first VEGF-targeted therapy. The clinical expert explained that more patients would be expected to have had pazopanib in the NHS, but the committee also heard that pazopanib and sunitinib have the same mechanism of action, although their adverse event profiles may differ. Because of this, the clinical expert did not consider the relatively low proportion of patients who have had pazopanib to affect the generalisability of the trial results to people seen in the NHS.
- More than half the patients in the trial had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and none had an ECOG performance status above 1. This reflected a fitter population than would generally be seen in the NHS, but the committee was aware that clinical trials normally include relatively fit patients who may not represent clinical practice.

The committee concluded that, overall, patients in HOPE 205 reflected people who would be offered second-line treatment in the NHS.

Differences in baseline characteristics between treatment groups

The differences between groups are based on small numbers of patients

3.8 The ERG identified some differences in the baseline characteristics of patients in the lenvatinib plus everolimus and everolimus alone groups, which may have resulted in a poorer prognosis in the latter group. For example, the ERG noted that, in the everolimus alone group, patients had a shorter duration of previous VEGF-targeted therapy, and complete or partial response to first-line VEGF-targeted therapy was documented in fewer patients. The clinical expert explained that the value of the duration of previous therapy as a prognostic indicator was debatable and the evidence weak. The committee understood that the ERG did not consider any individual difference in the characteristics at baseline to modify the effect of the study treatment, but that all differences taken together may introduce bias in favour of lenvatinib plus everolimus. The committee concluded that it could not assess the impact of the differences between the trial groups because they were based on small numbers of patients.

Clinical trial results

Lenvatinib plus everolimus increases progression-free survival

3.9 In HOPE 205, lenvatinib plus everolimus increased median progression-free survival in the intention-to-treat population by 9.1 months compared with everolimus alone (14.6 months compared with 5.5 months; hazard ratio 0.40, 95% confidence interval [CI] 0.24 to 0.68; p=0.0005). The committee noted that the results were similar for the post-hoc assessment of progression-free survival by independent review, though the difference between the treatment groups was smaller; median progression-free survival was 12.8 months with lenvatinib plus everolimus, and 5.6 months with everolimus alone, corresponding to a difference of 7.2 months

(HR 0.45, 95% CI 0.26 to 0.79; p=0.003). The committee noted that the investigators and the independent assessors disagreed in around one-quarter of patients as to whether or not the disease had progressed.

The trial was not powered to detect significant differences in overall survival

3.10 Overall survival was based on the latest data-cut of July 2015. Patients who had lenvatinib plus everolimus lived longer (median survival 25.5 months) than those who had everolimus alone (median survival 15.4 months), with a hazard ratio of 0.59 (95% CI 0.36 to 0.97). However, the p-value for the log rank test was not statistically significant (p=0.065). The committee was aware that the trial was not powered to detect significant effects between the treatment groups.

Lenvatinib plus everolimus is more effective than everolimus alone

3.11 The clinical expert commented that the increase in median progression-free survival with lenvatinib plus everolimus (9.1 months) is an impressive result. It exceeds that seen with first-line treatment when the cancer would be expected to respond better than in second-line treatment. Because of this, the clinical expert expressed their scepticism about the size of the benefit given the limitations of the trial and the absence of further data from other trials. The committee considered the possibility that greater benefit from second-line, rather than first-line, treatment could be attributed to the fact that the treatment, unlike most second-line treatments, comprises 2 drugs given together. But the clinical expert did not agree because a greater benefit on overall survival would be expected given the observed effect of lenvatinib plus everolimus on progression-free survival. The clinical expert noted that clinicians would be unlikely to prescribe lenvatinib plus everolimus over its comparators because of the clinical uncertainties introduced by the design and size of HOPE 205. The committee concluded that lenvatinib plus everolimus was more effective than everolimus alone with respect to progression-free survival and overall survival. However, the limitations of the trial, notably the small

number of patients, meant that the size of the benefit cannot be robustly estimated.

Safety

Lenvatinib plus everolimus leads to high toxicity

3.12 All patients had at least 1 treatment-emergent adverse event in the trial. Serious adverse events occurred in a higher proportion of patients taking lenvatinib plus everolimus (54.9%) than taking everolimus (42%). The committee noted that 72.5% of patients taking lenvatinib plus everolimus had grade III or higher treatment-emergent adverse events, compared with 54.0% taking everolimus. It was also aware that a larger proportion of patients had dose interruptions of lenvatinib (80.4%) or everolimus (76.5%) in the lenvatinib plus everolimus group compared with the everolimus alone group (54.0%), mainly because of adverse events. The committee considered it unsurprising that the combination (lenvatinib and everolimus) would be associated with more frequent adverse effects than everolimus alone. The clinical expert commented that the combination would be expected to increase the degree of toxicity of adverse events rather than their range compared with either individual drug. They considered that it would be difficult to offer a treatment that leads to grade III or IV adverse events in three-quarters of patients. The committee concluded that lenvatinib plus everolimus has a high burden of adverse events, and that it was important that the model adequately captures this.

Network meta-analysis

The company's revised network is appropriate for decision-making

3.13 Because there were no head-to-head trials comparing lenvatinib with axitinib, nivolumab or cabozantinib, the company compared the treatments indirectly using a network meta-analysis. It originally used the Bucher method, with everolimus as a common comparator. The company also presented a revised network meta-analysis which included only the

randomised controlled trials HOPE 205, CHECKMATE-025 and METEOR (lenvatinib plus everolimus, nivolumab and cabozantinib respectively, each compared with everolimus). The company assumed that axitinib was as effective as everolimus with respect to overall and progression-free survival, which the committee recognised was accepted in previous technology appraisals as a clinically reasonable assumption in this therapy area. The committee concluded that the company's revised network using fractional polynomials was appropriate for decision-making.

The model overestimated the progression-free survival benefit of lenvatinib plus everolimus compared with the observed effect

3.14 The committee discussed the modelled treatment effect over time after the end of the trial. It agreed that the data from HOPE 205 were relatively immature because, across the lenvatinib plus everolimus and everolimus alone groups, disease had progressed in only 62% of patients at the time of the analysis of progression-free survival, and only 45% of patients had died at the time of the analysis of overall survival. The committee noted that the progression-free survival hazard ratios dropped sharply (that is, the effect of lenvatinib plus everolimus increased relative to the comparators) around 2 months after starting treatment and then increased (the effect of lenvatinib plus everolimus decreased) before becoming constant. The committee agreed that this was implausible and highly unlikely in clinical practice. It considered the possibility that the Kaplan–Meier curves, being close at the beginning then diverging, resulted in a relationship between treatments that the fractional polynomials could not pick up. It further considered that piecewise modelling may have avoided this problem. The committee also looked at the trial-based fractional polynomial curves provided by the ERG to check the curve fits to the Kaplan–Meier data for lenvatinib plus everolimus and everolimus alone in HOPE 205. It agreed that the curves generally fitted the data well for progression-free and overall survival, although the curve for lenvatinib plus everolimus overestimated progression-free survival compared with the observed effect. The committee acknowledged the inherent

uncertainty associated with comparing treatments indirectly, which, when added to the other clinical uncertainties, meant that it could interpret the estimates of relative effectiveness only with caution.

Structure of the economic model

The model is suitable for decision-making

3.15 The company used a 3-stage, partitioned-survival economic model, which the committee considered appropriate to capture the natural history of the disease. The health states included in the model were pre-progressed disease, progressed disease and death. The company used data on time from randomisation to disease progression to determine the proportion of patients in the progression-free health state at a given time, and data on time to death to determine the proportion of patients who had reached the death state at a given time. The company calculated the proportion of patients in the post-progression health state as the difference between the proportion who had died and the proportion who had progressed. The committee concluded that the model was suitable for decision-making.

Modelling of clinical effectiveness

The survival curves generated using the ERG's own parameter values from the network meta-analysis are more appropriate than the company's curves

3.16 The committee discussed the extrapolation of progression-free survival and overall survival across the model time horizon (20 years) based on the company's network meta-analysis using fractional polynomials. The ERG considered that the company incorrectly applied fractional polynomials in its model, which resulted in an error when estimating survival probabilities. This caused the overall survival curves for each treatment to deviate implausibly around 60 months after starting treatment. To address this, the ERG generated fractional polynomial curves for the entire time horizon using its own parameter values from the network meta-analysis. The ERG's curves were largely similar to the

company's up to 5 years after starting treatment, but did not deviate later as seen with the company's curves. The committee noted that the company accepted their error, and concluded that it would consider the model with the ERG's correction.

Assuming the effect of lenvatinib plus everolimus continues for up to 20 years is highly uncertain

3.17 Both the company and the ERG assumed that the effect of lenvatinib plus everolimus continued beyond the trial follow-up, even after the disease progressed or people stopped treatment. But the committee noted that it was not presented with evidence to support this. The clinical expert considered that the treatment effect was unlikely to continue after progression with lenvatinib plus everolimus, but might do so with nivolumab because it is an immunotherapy. The committee concluded that assuming the effect of lenvatinib plus everolimus continues for up to 20 years, based on a trial with a median follow-up of under 3 years for overall survival, was highly uncertain.

Modelling treatment duration

The ERG's 2-knot spline distribution is suitable for modelling treatment duration

3.18 The committee recognised that the duration of each treatment assumed in the model determined the total cost of treatment. The ERG disagreed with how the company estimated the proportion of patients who continue to have any of the comparator treatments at any given cycle in the model. This was because the company implicitly assumed that the ratio of median treatment duration was the same as the ratio of the hazard rates for stopping treatment taken from the respective trial of each treatment, which the ERG considered incorrect. The ERG preferred fitting parametric distributions to the digitised Kaplan–Meier data. It noted that the 2-knot spline, followed by the log-normal distribution, best fit the curves. To validate the company and ERG's curves, the committee compared the

median time to stopping treatment estimated by the curves with that observed in the trial of the respective comparator treatment. The ERG's curves using the 2-knot spline distribution produced the closest estimate to the trial data. The committee concluded it would consider the model incorporating the ERG's 2-knot spline distribution.

Modelling health-related quality of life

Using utility values from the AXIS trial to model health-related quality of life is appropriate

3.19 The committee was aware that no data on health-related quality of life were collected in HOPE 205, and that the company used utility values from the AXIS trial, comparing axitinib with sorafenib for advanced renal cell carcinoma (0.69 for the pre-progressed disease states and 0.61 for the progressed disease states). AXIS has been accepted as a valid source of utility data for this patient population in recent NICE technology appraisals. The committee concluded that the utility values from AXIS were appropriate.

The utility values used in the model do not reflect quality of life appropriately

3.20 To estimate the impact of adverse events on health-related quality of life, the company deducted a decrement (an amount reflecting the effect of adverse events on health-related quality of life) from the baseline utility values from AXIS. It estimated the total utility decrements separately for each 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 company derived a total utility decrement of −0.013 for lenvatinib plus everolimus, −0.003 for everolimus, −0.010 for axitinib, −0.011 for cabozantinib, and −0.002 for nivolumab. The ERG commented that the value of 0.69 used in the company's base case already includes the impact of adverse events on quality of life. This means that there is double counting of decrements, for axitinib at least.

The committee recalled that lenvatinib plus everolimus is associated with a high rate of serious adverse events (see section 3.12) and that the utility values used in the model should reflect this. However, the utility decrement for lenvatinib plus everolimus was small. It did not reflect the adverse event profile of lenvatinib plus everolimus, not least because it did not correlate with the observation in HOPE 205 that all patients who had lenvatinib plus everolimus had an adverse event, and that many stopped treatment because of these adverse events. The clinical expert shared the committee's concern, noting that the utility decrements applied by the company contradicted the available evidence on the safety of lenvatinib plus everolimus. The committee concluded that the utility values used in the model did not reflect quality of life appropriately.

Cost and effect of subsequent treatments

The company or the ERG's approach is reasonable for modelling subsequent treatments

3.21 The company did not originally include the cost of subsequent therapies in its model. In response to a request for clarification from the ERG, the company chose to estimate the cost of subsequent therapies (that is, third-line treatment and beyond) based on the UK market share of the drugs. The company justified this on the basis that using real-world evidence is more robust than using trial data, the trials were not done at the same time, and many comparators were not available when the trials were done. In contrast, the ERG argued that it was more appropriate to base these costs on the proportions of subsequent treatments received in the included trials for lenvatinib plus everolimus and for all comparators. The committee noted that either approach had little impact on the results. Although the committee appreciated that there may be arguments for using the company or the ERG's costs of subsequent treatment, it concluded that either approach could be considered suitable for decision-making.

Results of the cost-effectiveness analyses

The ERG's base case is more appropriate for decision-making

3.22 The committee considered the cost-effectiveness results from the base case using the company's model and the model with the ERG's amendments, including confidential discounts for all technologies. It agreed that the ERG's base case was more appropriate for decision-making because it used:

- the ERG's preferred survival curves: best fitting fractional polynomials for overall survival and progression-free survival in the company's base case (see section 3.16)
- the ERG's 2-knot spline approach for modelling treatment duration (see section 3.18).

Lenvatinib plus everolimus does not meet the end-of-life criteria compared with current NHS treatment

3.23 The committee considered the advice about life-extending treatments for people with a short life expectancy in NICE's final Cancer Drugs Fund technology appraisal process and methods. The company stated in its submission that it did not believe that lenvatinib plus everolimus is suitable for consideration as a life-extending treatment at the end of life. The committee noted that the model results of the ERG base case suggested that lenvatinib plus everolimus met the criterion for short life expectancy compared with axitinib, but not compared with cabozantinib or nivolumab. However, the committee recognised that in clinical practice people with advanced renal cell carcinoma are likely to have a life expectancy of more than 24 months because, after positive NICE guidance on nivolumab and cabozantinib, there are now more life-extending treatment options available after disease progression than when the clinical trials were done. The ERG's base case suggested that lenvatinib plus everolimus was likely to extend mean overall survival by more than 3 months compared with axitinib, cabozantinib and nivolumab. However, the

committee had concerns about the quality and robustness of the analyses it had seen, particularly with regard to the modelling of treatment effectiveness, treatment duration and the impact of adverse events on quality of life. Because of this, the committee did not consider the estimates produced by the model to be reliable enough for it to conclude on this. The committee therefore concluded that lenvatinib plus everolimus did not meet the end-of-life criteria compared with current NHS treatment.

Lenvatinib plus everolimus is not a cost-effective use of NHS resources

3.24 The committee noted that, in the ERG's base-case analysis, cabozantinib was extendedly dominated by axitinib and lenvatinib plus everolimus, and lenvatinib plus everolimus dominated nivolumab. The incremental cost-effectiveness ratio (ICER) for lenvatinib plus everolimus compared with axitinib was much higher than £30,000 per quality-adjusted life year. Although the committee preferred the ERG's base case, it still had concerns about the validity of the results, particularly:

- the modelling of treatment effectiveness (see section 3.17)
- the duration of treatment assumed in the model (see section 3.18)
- the utility values (see sections 3.19 and 3.20).

Given the high ICERs and the substantial uncertainty in the results, the committee concluded that it could not recommend lenvatinib plus everolimus as a cost-effective use of NHS resources.

Other factors

3.25 The Pharmaceutical Price Regulation Scheme (2014) payment mechanism was not relevant in considering the cost effectiveness of technology.

3.26 The committee discussed whether lenvatinib plus everolimus was an innovative treatment. The company argued that lenvatinib plus everolimus is considered innovative because the combination has shown a

synergistic effect whereby the 2 treatments together lead to higher efficacy levels with respect to progression-free survival and response rate than each of the individual treatments. The committee noted that the clinical expert did not consider lenvatinib plus everolimus to be a step-change in managing the condition. It agreed that lenvatinib plus everolimus was unlikely to fulfil an unmet clinical need in a particular group of people. The committee concluded that there was no benefit to utility that was not otherwise accounted for in the modelling.

4 Proposed date for review of guidance

4.1 NICE proposes that the guidance on this technology is considered for review by the guidance executive 3 years after publication of the guidance. NICE welcomes comment on this proposed date. The guidance executive will decide whether the technology should be reviewed based on information gathered by NICE, and in consultation with consultees and commentators.

Amanda Adler
Chair, Appraisal Committee
July 2017

5 Appraisal committee members and NICE project team

Appraisal committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by committee B.

Committee members are asked to declare any interests in the technology to be appraised. If it is considered there is a conflict of interest, the member is excluded from participating further in that appraisal.

The minutes of each appraisal committee meeting, which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

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NICE project team

Each technology appraisal is assigned to a team consisting of 1 or more health technology analysts (who act as technical leads for the appraisal), a technical adviser and a project manager.

Orsolya Balogh
Technical Lead

Ahmed Elsada
Technical Adviser

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