NICE National Institute for Health and Care Excellence

NICE guidance

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma

Technology appraisal guidance

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Your responsibility

The recommendations in this guidance represent the view of NICE, arrived at after careful consideration of the evidence available. When exercising their judgement, health professionals are expected to take this guidance fully into account, alongside the individual needs, preferences and values of their patients. The application of the recommendations in this guidance are at the discretion of health professionals and their individual patients and do not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian.

Commissioners and/or providers have a responsibility to provide the funding required to enable the guidance to be applied when individual health professionals and their patients wish to use it, in accordance with the NHS Constitution. They should do so in light of their duties to have due regard to the need to eliminate unlawful discrimination, to advance equality of opportunity and to reduce health inequalities.

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible.

Contents

1 Recommendations

1.1 Lenvatinib plus everolimus is recommended as an option for treating advanced renal cell carcinoma in adults who have had 1 previous vascular endothelial growth factor (VEGF)-targeted therapy, only if:

- their Eastern Cooperative Oncology Group (ECOG) performance status score is 0 or 1 and
- the company provides lenvatinib with the discount agreed in the patient access scheme.

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

In the NHS, advanced renal cell carcinoma that has progressed after 1 tyrosine kinase inhibitor is treated with axitinib, nivolumab or cabozantinib. The evidence from a single clinical trial suggests that, on average, people live around 10.1 months longer if they have lenvatinib plus everolimus rather than everolimus alone. In the trial, lenvatinib plus everolimus caused side effects, leading many patients to interrupt or even stop treatment. This is despite the patients enrolled in the trial being relatively fit (that is, they had an ECOG performance status score of 0 or 1).

The cost-effectiveness analyses for lenvatinib plus everolimus show it's more effective and less costly than cabozantinib and nivolumab. Compared with axitinib, the cost-effectiveness estimates are within what NICE normally considers acceptable. So, NICE is recommending lenvatinib plus everolimus as an option for use in the NHS in people with an ECOG performance status score of 0 or 1.

2 Information about lenvatinib

Marketing authorisation	Lenvatinib (Kisplyx, Eisai) is indicated 'in combination with everolimus for the treatment of adult patients with advanced renal cell carcinoma following one prior vascular endothelial growth factor (VEGF)-targeted therapy'.
Dosage in the marketing authorisation	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. This scheme provides 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 does not constitute an excessive administrative burden on the NHS.

3 Committee discussion

The appraisal committee (see 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 (a TKI), nivolumab (a programmed cell death protein 1 [PD-1] inhibitor), cabozantinib (a TKI), or everolimus (a mammalian target of rapamycin [mTOR] inhibitor), as recommended in NICE technology appraisal guidance. 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 than second or third line in the treatment pathway so that everolimus would be mainly 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 vascular endothelial growth factor (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 as a fourth-line treatment (see section 3.1). The committee noted that the final scope 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 trial did not allow crossover. 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

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 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 the company submitted it for regulatory approval because it considered the reported results to be compelling. The committee recognised that, because the trial had a pre-determined 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 these estimates were less clear than if the trial had included more patients.

  The committee concluded that, given the clinical evidence to date, the results of HOPE 205 need to be interpreted with caution.

Dose

The modelled dose of lenvatinib plus everolimus should mirror HOPE 205

3.6 In HOPE 205, the median daily dose of lenvatinib was 13.6 mg, only 75% of the approved daily dose in the marketing authorisation of 18 mg. The company explained that it has an ongoing trial comparing the recommended dose of lenvatinib (18 mg) with a lower dose (14 mg), to assess whether the same efficacy can be achieved with improved tolerability. The clinical expert took this to suggest that there was uncertainty around the optimal dose of lenvatinib. The committee concluded that it can appraise lenvatinib only at its licensed dose, and that the modelled dose should appropriately reflect the estimates on the effectiveness and safety of lenvatinib plus everolimus from HOPE 205.

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 people who would have lenvatinib in the NHS, noting that 11 of the 37 study sites were in the UK. In particular, it discussed the following 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 people would be expected to have pazopanib in the NHS than they did in the trial because clinicians perceive pazopanib to have a better safety profile than sunitinib. However, the 2 drugs have the same mechanism of action, and so the clinical expert did not consider that the relatively low proportion of patients who had pazopanib in the trial would affect the generalisability of the results to people seen in the NHS.
- More than half the patients in the trial had an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, and none had an ECOG performance status score above 1. This reflected a fitter population than would generally be seen in the NHS. Although the committee was aware that clinical trials normally include relatively fit patients who may not represent clinical practice, it concluded that this was an important issue in this appraisal because people may need to be fit to be able to tolerate lenvatinib plus everolimus.

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

Clinical trial results

Lenvatinib plus everolimus increases progression-free survival compared with everolimus alone

3.8 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 [HR] 0.40, 95% confidence interval [CI] 0.24 to 0.68; p=0.0005). The committee noted that progression-free survival assessed post hoc by independent review

was similar, 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. However, both assessments of disease progression suggested that lenvatinib plus everolimus was more effective than everolimus alone with respect to progression-free survival.

The evidence that lenvatinib extends overall survival is statistically weak

3.9 Overall survival was based on the latest data cut of July 2015 (a median follow-up of 32.0 months for lenvatinib plus everolimus and of 32.7 months for everolimus alone). Patients who had lenvatinib plus everolimus lived longer than those who had everolimus alone (median survival 25.5 months versus 15.4 months; HR 0.59, 95% CI 0.36 to 0.97, based on the stratified Cox proportional hazard model). The p value using the stratified log-rank test was 0.065, which the committee recognised reflected statistically weak evidence on the survival benefit with lenvatinib plus everolimus. However, it was aware that HOPE 205 was not powered to detect statistically significant differences in terms of overall survival between treatment groups.

Lenvatinib plus everolimus is more effective than everolimus alone but the size of the benefit is unclear

3.10 The ERG identified differences in the characteristics of patients and the disease at baseline, which suggested that patients in the lenvatinib plus everolimus group had a better prognosis that those in the everolimus group. For example, compared with the everolimus alone group, patients in the lenvatinib plus everolimus group had had previous VEGF-targeted therapy for longer, and were more likely to have had a complete or partial response to first-line VEGF-targeted therapy. The clinical expert explained that duration of previous therapy as a prognostic indicator was debatable and the evidence weak. The committee noted that the tumour burden was greater in patients randomised to lenvatinib plus everolimus than in those randomised to everolimus alone. It understood that the ERG did not consider that any individual difference in the characteristics 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. This affected the precision with which the benefit of lenvatinib plus everolimus was estimated.

The size of the benefit with lenvatinib plus compared with current NHS treatments cannot be robustly estimated

3.11 The clinical expert questioned the face validity of the increase in median progression-free survival in HOPE 205 with lenvatinib plus everolimus (9.1 months) because it exceeds that seen with first-line treatments (when cancer would be expected to respond better than to second-line treatment). The committee considered that this greater than expected benefit with first-line treatments could have resulted from lenvatinib plus everolimus being 2 treatments rather than 1 treatment. The clinical expert did not agree with this proposition because lenvatinib plus everolimus would have also been expected to be associated with benefits on overall survival in excess of first-line therapies. The clinical expert commented that clinicians would be unlikely to prefer lenvatinib plus everolimus to its comparators because of the uncertainties introduced by the design and size of HOPE 205. The committee concluded that the limitations of the trial, notably the small number of patients and a comparator not routinely used in the NHS, meant that the size of the benefit compared with current NHS treatments could not be robustly estimated.

Safety

Lenvatinib plus everolimus has more side effects than lenvatinib or everolimus alone

3.12 The committee considered the safety profile of lenvatinib plus everolimus, noting that:

- Serious adverse events occurred in a higher proportion of patients taking lenvatinib plus everolimus (54.9%) than in patients taking everolimus alone (42.0%).
- In the lenvatinib plus everolimus group, 72.5% of patients had grade III or higher treatment-emergent adverse events, compared with 54.0% of patients taking everolimus alone.

- 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.
- Patients in HOPE 205 had treatment until disease progression, unacceptable toxicity or withdrawal of consent. The median time to stopping treatment (7.6 months) was half the median progression-free survival (14.6 months) in the trial, which suggested that many patients did not tolerate lenvatinib plus everolimus.

It is important to take performance status into account

3.13 The committee considered it unsurprising that the combination of lenvatinib plus 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 the range of toxicity compared with either individual drug. The clinical expert also considered that it would be difficult to offer people a treatment that would lead to grade III or IV adverse events in three-quarters of them. The committee recalled that HOPE 205 included only patients with an ECOG performance status score of 0 or 1. It considered that people with worse performance status would be less likely to tolerate lenvatinib plus everolimus than patients in the trial. As a result, the effect of treatment seen in the trial was unlikely to be seen in people with lower performance status, partly because they would not have had treatment long enough to derive the same benefits. 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 that it was important to consider performance status in the decision-making.

Network meta-analysis

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

3.14 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 included the randomised controlled trials HOPE 205, CHECKMATE-025 and METEOR (lenvatinib plus everolimus, nivolumab and cabozantinib respectively, each compared with everolimus), and

estimated overall and progression-free survival curves for each treatment using fractional polynomials, as described by Janssen et al. (2011). In doing so, the company assumed that axitinib was as effective as everolimus with respect to overall and progression-free survival, which the committee recalled it had accepted in previous technology appraisals as a reasonable assumption in this therapy area. The committee concluded that the company's network using fractional polynomials was appropriate for decision-making.

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

3.15 The data from HOPE 205 were relatively immature at the time of the analysis of progression-free survival (June 2014) because, across the lenvatinib plus everolimus and everolimus alone groups, disease had progressed in only 62% of patients. The modelled treatment effectiveness showed 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. The committee examined 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 how the curves fitted the progression-free and overall survival data was generally acceptable, 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 other clinical uncertainties, meant that it could interpret the estimates of relative effectiveness only with caution.

Structure of the economic model

The structure of the model is suitable for decision-making

3.16 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

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

3.17 The committee discussed the extrapolation of progression-free 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 the start of treatment. To address this, the ERG generated fractional polynomial curves for the entire time horizon using its own parameter values from its own 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 acknowledged its error, and concluded that it would consider the model with the ERG's correction.

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

3.18 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. The committee was not presented with evidence to support this. The clinical expert considered that the treatment effect on overall survival was unlikely to continue after progression with lenvatinib plus everolimus, but might do so with the comparator nivolumab because it is an immunotherapy. The committee recalled that the evidence base

underpinning the extrapolation was already uncertain (see section 3.9). It 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. It would have liked to have seen more conservative assumptions explored, for example, that the effect of treatment ceased at the end of the trial, or diminished over time beyond the trial follow-up.

Modelling treatment duration

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

3.19 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 continued on any of the comparator treatments at any given cycle in the model. The company assumed that the ratio of median duration of treatment equalled 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 digitised Kaplan–Meier data from each trial. The committee noted that the 2-knot spline, followed by the log-normal distribution, best fitted 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 seen in the trials of the comparator treatments. 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

3.20 The committee was aware that the HOPE 205 trial did not collect data on health-related quality of life, and that the company used utility values from the AXIS trial, which had compared axitinib with sorafenib for advanced renal cell carcinoma. The utility values from AXIS were 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 other

NICE technology appraisals in this disease area. The committee concluded that the utility values from AXIS were appropriate.

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

3.21 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 estimates incorporated the average duration of each adverse event, taken directly from the HOPE 205 study for lenvatinib plus everolimus and estimated from the respective clinical trials for the comparators. In response to the appraisal consultation document, the company revised its utility decrements to −0.097 for lenvatinib plus everolimus, −0.072 for axitinib, −0.084 for cabozantinib and −0.008 for nivolumab. The committee recalled that the utility values used in the model should have reflected the high rate of serious adverse events associated with lenvatinib plus everolimus (see section 3.12). However, the 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 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. Furthermore, the Cancer Drugs Fund clinical lead pointed out that the revised utility decrement for nivolumab also appeared too small given its immunotoxicity. 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's and the ERG's approaches are reasonable for modelling subsequent treatments

3.22 The company did not originally include in its model the cost of therapies patients had in HOPE 205 after stopping study treatment. 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. In contrast, the ERG argued that it was better to base these costs on the proportions of subsequent treatments in the 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 than the company's

3.23 The committee considered the cost-effectiveness results from the company's base case and the ERG's base case, including confidential discounts for all technologies. It noted that, in response to the appraisal consultation document, the company revised its patient access scheme discount. It agreed that the ERG's base case was more appropriate for decision-making because it used:

- the ERG's own best-fitting fractional polynomials for overall and progression-free survival (see section 3.17)
- the 2-knot spline distribution to model treatment duration (see section 3.19).

However, the committee recognised that the ERG's base case did not reflect all of its preferred analyses because:

- it assumed that the effect of lenvatinib plus everolimus continues until the end of the time horizon of 20 years (see section 3.18)
- the utility decrement for lenvatinib plus everolimus was too small given the incidence and severity of adverse events that occurred in HOPE 205 (see section 3.21).

The committee concluded that it would use the ERG's base case for decision-making.

Lenvatinib plus everolimus is a cost-effective use of NHS resources in people with an ECOG performance status score of 0 or 1

3.24 The committee noted that, in the ERG's deterministic base-case analysis, lenvatinib plus everolimus dominated cabozantinib and nivolumab, that is it was

more effective and less costly. The incremental cost-effectiveness ratio for lenvatinib plus everolimus compared with axitinib was between £20,000 and £30,000 per quality-adjusted life year, which is the range normally accepted by NICE to represent cost-effective technologies. The committee appreciated that the uncertainty in the cost-effectiveness estimates came mainly from the limitations of HOPE 205 (see section 3.5), and from the modelling assumptions about the long-term performance of treatment (see section 3.18) and the impact of adverse events on health-related quality of life (see section 3.21). The committee also considered the value patients and clinicians place on having treatment options. On balance, the committee agreed that lenvatinib plus everolimus could be recommended for previously treated advanced renal cell carcinoma. It recalled that the evidence it had seen reflected patients with an ECOG performance status score of 0 or 1; less fit people would be less likely to tolerate treatment, and would be unlikely to derive the same benefits seen in HOPE 205 (see section 3.13). This meant that lenvatinib plus everolimus was unlikely to be cost effective in people with an ECOG performance status score above 1. The committee concluded that it could recommend lenvatinib plus everolimus, but only for people with an ECOG performance status score of 0 or 1.

Other factors

Future research

3.25 The committee heard that the company is considering an observational study to gather further data on the safety and quality of life of lenvatinib plus everolimus, aiming to have the results by 2020. The company said that this study is still in the early stages of development and that, while it might include comparators used in routine clinical practice, these are not yet defined. The committee understood that the study might include UK sites. It agreed that it had too little information about the study to enable it to determine its value. However, the committee encouraged further data collection on lenvatinib plus everolimus because this could provide comparative evidence against established NHS practice in England.

Innovation

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 Implementation

4.1 Section 7(6) of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 requires clinical commissioning groups, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this appraisal within 3 months of its date of publication.

4.2 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal recommends the use of a drug or treatment, or other technology, the NHS in Wales must usually provide funding and resources for it within 2 months of the first publication of the final appraisal determination.

4.3 When NICE recommends a treatment 'as an option', the NHS must make sure it is available within the period set out in the paragraphs above. This means that, if a patient has previously treated advanced renal cell carcinoma and the doctor responsible for their care thinks that lenvatinib plus everolimus is the right treatment, it should be available for use, in line with NICE's recommendations.

4.4 The Department of Health and Eisai have agreed that lenvatinib will be available to the NHS with a patient access scheme which makes it available with a discount. The size of the discount is commercial in confidence. It is the responsibility of the company to communicate details of the discount to the relevant NHS organisations. Any enquiries from NHS organisations about the patient access scheme should be directed to cyndy_simon@eisai.net.

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.

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.

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Accreditation