

Cabozantinib for previously treated advanced renal cell carcinoma

Technology appraisal guidance

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1 Recommendations

- 1.1 Cabozantinib is recommended, within its marketing authorisation, as an option for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF)-targeted therapy, only if the company provides cabozantinib with the discount agreed in the patient access scheme.

2 The technology

Description of the technology	Cabozantinib (Cabometyx, Ipsen) is a small molecule that inhibits multiple receptor tyrosine kinases.
Marketing authorisation	Cabozantinib 'is indicated for the treatment of advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy'.
Adverse reactions	The most common serious adverse reactions associated with cabozantinib are abdominal pain (3%), pleural effusion (3%), diarrhoea (2%) and nausea (2%). For full details of adverse reactions and contraindications, see the summary of product characteristics.
Recommended dose and schedule	Administered orally, 60 mg once daily.
Price	<p>The list price is £5,143.00 per 30-tab pack applicable to all dosages (20 mg, 40 mg and 60 mg).</p> <p>The company has agreed a patient access scheme with the Department of Health. This scheme provides a simple discount to the list price of cabozantinib, 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.</p>

3 Evidence

The appraisal committee ([section 6](#)) considered evidence submitted by Ipsen and a review of this submission by the evidence review group. See the [committee papers](#) for full details of the evidence.

4 Committee discussion

The appraisal committee reviewed the data available on the clinical and cost effectiveness of cabozantinib, having considered evidence on the nature of renal cell carcinoma and the value placed on the benefits of cabozantinib by people with the condition, those who represent them, and clinical experts. It also took into account the effective use of NHS resources.

- 4.1 The committee was aware that, despite new treatments recently being recommended by NICE, there remained an unmet clinical need for some people with advanced renal cell carcinoma. It noted that the clinical experts perceived cabozantinib to be more effective than everolimus and axitinib, although it caused more adverse effects. The committee recognised that people with advanced renal cell carcinoma would value any increased life expectancy offered by cabozantinib and may be prepared to tolerate the adverse effects of treatment.

Treatment pathway

- 4.2 The committee heard from the clinical experts that most people in the NHS with newly diagnosed advanced renal cell carcinoma will first be offered 1 of 2 tyrosine kinase inhibitors (TKIs), [pazopanib](#) or [sunitinib](#), as recommended in NICE guidance. If the disease progresses and they are fit enough to have further treatment, most people are then offered [axitinib](#) (also a TKI), [nivolumab](#) (a programmed cell death protein 1 [PD-1]), or [everolimus](#) (a mammalian target of rapamycin [mTOR] inhibitor), as recommended in NICE guidance. If the disease progresses again, people who previously had axitinib may have nivolumab or everolimus as a third-line treatment; people who had nivolumab may have axitinib or everolimus; and people who had everolimus may have axitinib or nivolumab. The committee was aware that some patients have fourth-line treatment and beyond, but that no accepted treatment pathway exists at this point. It concluded that the current treatment pathway offered options for patients.

- 4.3 The committee was aware of the recent changes in the

recommendations for everolimus, and discussed the impact of these on the treatment pathway. At the first committee meeting, it heard from the clinical experts that everolimus could be used after 1 previous treatment (second line), although they would prefer to use it after 2 or 3 previous treatments (third or fourth line). At that time, everolimus was available only through the Cancer Drugs Fund, as a second-line treatment, after 1 TKI for people who cannot have axitinib. So, clinicians could not use everolimus beyond the second-line setting in the NHS. NICE published [guidance following the Cancer Drugs Fund reconsideration of everolimus](#) in February 2017, recommending everolimus, with a new patient access scheme (lower price), for routine commissioning. The Cancer Drugs Fund reconsideration of everolimus broadened the population eligible for treatment. It means that everolimus is now recommended after 1 or more lines of vascular endothelial growth factor (VEGF)-targeted therapy (which includes TKIs), rather than after only 1 TKI in those who cannot take axitinib. Given the clinicians' preference to use everolimus later in treatment, the committee appreciated that use of everolimus after the recommendation changes was likely to shift down the treatment pathway. Responses to the second consultation echoed this view. The committee concluded that everolimus was predominantly used in clinical practice after 3 previous treatments (including nivolumab and axitinib), that is as a fourth- or subsequent-line treatment.

Population and comparators

- 4.4 The clinical experts explained that they would offer cabozantinib to patients who have had 1 or 2 previous treatments. The committee recalled that, at this point, axitinib and nivolumab are also treatment options (see [section 4.2](#)), but not everolimus, which would be used after these treatments (see [section 4.3](#)). The committee was aware that the final scope of this appraisal included best supportive care as a comparator. It heard from the clinical experts that active treatment is unsuitable for a small group of people who are not fit enough and who will instead have best supportive care. The committee appreciated that, after positive NICE guidance on nivolumab, this group was even smaller, and unlikely to reflect those who would be offered cabozantinib. It concluded that cabozantinib would be used in people who have had 1 or 2 previous treatments, and that the relevant comparators were

axitinib and nivolumab.

- 4.5 The committee discussed whether there was merit in considering separately people who have had 1 or 2 previous treatments. It heard from the clinical experts that there was no biological reason for axitinib to work any differently based on people having 1 or 2 previous treatments. In addition, the clinical experts stated that cabozantinib would be expected to work similarly after 1 previous treatment as it would after 2 previous treatments, and that it would also work after other TKIs had failed. The committee concluded that it would consider cabozantinib for the population comprising people who have had either 1 or 2 previous treatments as a whole.

Clinical effectiveness

- 4.6 The committee noted that the main evidence for cabozantinib came from METEOR, an open-label randomised controlled trial comparing cabozantinib with everolimus. It appreciated that the trial did not allow patients to switch from everolimus to cabozantinib at disease progression. The committee heard from the clinical experts that the results of METEOR were generalisable to the NHS.
- 4.7 The committee noted that METEOR measured progression-free survival in 2 populations:
- The primary endpoint intention-to-treat population: the first 375 patients randomised (n=375).
 - The intention-to-treat population: all patients randomised at baseline (n=658).

The committee noted that more events occurred in the intention-to-treat population than in the primary endpoint intention-to-treat population, which resulted in more mature data. It also noted that the intention-to-treat population reflected a longer follow-up than the primary endpoint intention-to-treat population. Because of this, the committee concluded that it would use the intention-to-treat population analysis for its decision-making.

Clinical trial results

4.8 In the intention-to-treat population of METEOR (December 2015 data cut-off):

- Progression-free survival improved with cabozantinib compared with everolimus (median 7.4 and 3.9 months respectively; hazard ratio 0.51; 95% confidence interval [CI] 0.41 to 0.62; $p < 0.0001$).
- Overall survival improved with cabozantinib compared with everolimus (median 21.4 and 16.5 months respectively; hazard ratio 0.66; 95% CI 0.53 to 0.83; $p = 0.00026$).

The committee also noted the updated survival data from METEOR, presented by the company in response to the first consultation (based on a cut-off date of October 2016), and welcomed the availability of new, more mature data. It concluded that cabozantinib was more effective than everolimus in METEOR.

Network meta-analysis

4.9 Because there were no head-to-head trials comparing cabozantinib with axitinib or nivolumab, the company did a network meta-analysis to compare the treatments indirectly. The original network linked 6 trials, including TARGET, which compared sorafenib with placebo. Although sorafenib was not a comparator for cabozantinib in this appraisal, the company included TARGET to link together treatments. The committee was concerned about including this trial for 2 reasons. First, none of the patients had previously had VEGF-targeted therapies. Second, the company used immature data from the trial, which censored patients who switched from placebo to sorafenib. This was likely to have underestimated the effect of sorafenib because the placebo data reflected patients whose disease responded relatively well (who were therefore not censored), and this would in turn have underestimated the effect of axitinib. In response to the first consultation, and in line with the committee's preference, the company submitted a revised network that excluded TARGET. This assumed that axitinib was as effective as everolimus in terms of overall and progression-free survival. The committee concluded that the company's simplified network reduced the potential bias associated with using immature data from TARGET.

Methodology of the network meta-analysis

4.10 The committee understood that, to estimate long-term outcomes, the company used a 'family' of related survival curves for cabozantinib and for all of the comparator treatments. The company chose the curves based on how well, on average, they fitted the data on overall or progression-free survival for all the treatments in the network. The committee noted that, because of this simplification, the parametric distribution chosen by the company for both progression-free and overall survival (log-normal for both endpoints) did not fit the data for each individual treatment well. In response to the first consultation, the company used fractional polynomial modelling, as described by Janssen et al. (2011), to fit survival curves. The new method also used a family of related survival curves for all the treatments. However, the committee agreed that it was a more flexible family, which improved the curve fits to the Kaplan–Meier data on overall and progression-free survival for all treatments in the network compared with the original parametric modelling using the log-normal distribution. The committee appreciated that the fractional polynomial modelling did not fit data in the extrapolation period. It noted that the evidence review group (ERG) considered that estimating survival based on the 'average fit' across the network (as opposed to the fit for each individual treatment) was less of an issue with fractional polynomial models than with parametric curve fitting. The committee was satisfied that the company's revised modelling of overall and progression-free survival was more appropriate than the original parametric modelling.

Cost effectiveness

4.11 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 the model to estimate average delay in time to disease progression, average delay in time to death, and costs and health-related quality of life associated with cabozantinib and its comparators by forecasting beyond the end of the trials. The modelled population reflected the trial population of METEOR in that it included people who had had 1 (71%), or

2 or more (29%), previous treatments. This was consistent with the population who would have cabozantinib in clinical practice (see [section 4.4](#)).

4.12 In its original submission, the company presented 2 separate cost-effectiveness analyses based on the model:

- A trial-based analysis comparing cabozantinib with everolimus using data from METEOR only.
- A network meta-analysis-based analysis comparing cabozantinib with axitinib, everolimus, best supportive care and nivolumab using data from the network meta-analysis.

In response to the first consultation, the company revised the network meta-analysis to exclude best supportive care, in line with the committee's conclusion about the treatment pathway (see [section 4.3](#)). The committee recognised that the trial data were more robust than those estimated from the network meta-analysis because they reflected a direct comparison between 2 treatments. The committee acknowledged that everolimus was not a relevant comparator for cabozantinib for most patients. Nevertheless, it agreed that it could have confidence that the model was suitable for decision-making with respect to axitinib and nivolumab if, based on the network meta-analysis (using fractional polynomial survival modelling), it produced plausible estimates for cabozantinib compared with everolimus that aligned with the analysis based on observed data from METEOR (using parametric survival modelling). Although the company, in response to the first consultation, did not present a trial-based analysis, the committee heard from the ERG that there was little difference between the results of the trial-based and the network meta-analysis-based analyses. The committee was therefore satisfied that the comparisons of cabozantinib with axitinib and nivolumab were reliable.

Survival modelling

4.13 The committee considered the company's revised modelling in response to the first consultation. It noted that, to estimate overall and progression-free survival for cabozantinib and its comparator treatments, the company extrapolated the curves based on fitting fractional

polynomial models (see [section 4.10](#)) up to the end of the time horizon. As such, to estimate overall and progression-free survival for cabozantinib and its comparator treatments, the company used fractional polynomial modelling during both the trial follow-up and extrapolation. Hereafter, this analysis will be referred to as 'the company's revised base case'.

Comparison of survival predictions in the company's revised base case with observational data on everolimus (the natural history of the disease)

4.14 In its revised base case (see [section 4.13](#)), the company predicted that 5% of people in the everolimus arm would be alive 5 years after starting treatment. The committee compared this estimate with 2 sources of observational data submitted during the first consultation:

- Registry-based pharmaco-epidemiological data from a publication by Ruiz-Morales et al. (2016) submitted by the company. These data came from the International Metastatic renal cell carcinoma Database Consortium (IMDC) reflecting people initially treated with either pazopanib or sunitinib. Some people then had second-line treatment. The company presented data for people who had second-line treatment after sunitinib (n=2,667) because this group was larger than the group that had second-line treatment after pazopanib (n=260). It noted that, in this group, about 10% were alive 5 years after starting treatment.
- Audit data from the Christie Hospital (Manchester, UK) submitted by a clinical expert. These data showed that, among people who had axitinib or everolimus as a second-line treatment (n=282), around 6% were alive 5 years after starting treatment.

4.15 The committee discussed whether the Ruiz-Morales et al. (2016) data on were generalisable to patients who would be offered everolimus in the UK. It observed that:

- Ruiz-Morales et al. did not include patients from the UK. The committee acknowledged that the company considered that this study included people with similar characteristics at baseline to patients in METEOR, and that the

countries from which these people were included had similar socio-economic profiles and health systems to the UK.

- As second-line treatment, only 45% of people had everolimus, and some had treatments that were not available in the NHS.
- Ruiz-Morales et al. did not report information on the third-line treatments; these treatments may not be available in the NHS, and may have biased the effect of second-line treatment.

For these reasons, the committee agreed that the survival estimates from Ruiz-Morales et al. were likely to overestimate the survival of patients who have everolimus in the NHS. It considered the 5-year survival estimate from the Christie Hospital audit to be unreliable because the numbers were small and there were no observations beyond 3 years 3 months after starting treatment. The committee concluded that survival in the UK was likely to have been overestimated in Ruiz-Morales et al., but it did provide useful data with which to compare the survival prediction of the company's model.

- 4.16 The committee noted that the company presented a scenario analysis to align the revised base-case predictions (see [section 4.14](#)) and the data from Ruiz-Morales et al. (2016). In this, the company did not change the modelling of progression-free survival, that is, it continued to use fractional polynomial modelling across the entire time horizon. For overall survival, it used fractional polynomial modelling during the trial follow-up period (as per the revised base case), but used parametric modelling choosing the log-normal distribution during the extrapolation period. The committee noted that this scenario aligned the model's predictions of survival with data from Ruiz-Morales et al. However, the committee did not consider that it was appropriate to base the extrapolation on meeting the 5-year death rate observed in Ruiz-Morales et al. The committee recalled that survival among people having everolimus was likely to have been overestimated in Ruiz-Morales et al. It concluded that it preferred the company's revised base case, which used fractional polynomial modelling across the entire time horizon for both overall and progression-free survival.

Duration of cabozantinib's treatment effect

- 4.17 The committee noted that both the company and the ERG assumed that the effect of cabozantinib continued beyond the trial follow-up, even after the disease progressed or patients stopped treatment, but the committee was not presented with evidence to support this. The clinical experts considered that it was not clear whether a survival benefit would continue after stopping treatment. They explained that, in clinical practice, some patients have stable disease for 2 to 3 years after stopping treatment, whereas the disease progresses more quickly in others. Also, some patients have a prolonged response after a short length of treatment and others do not. The committee concluded that assuming the effect of cabozantinib continues for up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival, was highly uncertain.

Modelling of nivolumab

- 4.18 The committee noted that, for nivolumab, the company's revised base case (see [section 4.13](#)) estimated a longer progression-free survival than overall survival. It understood that, in the model, disease progression could occur until the point where overall and progression-free survival curves cross (around 5 years after starting treatment), after which people whose disease had not progressed followed the overall survival curve. This meant that the company assumed that the disease would never progress at that point, instead people would die of causes other than their cancer. It also meant that they would accrue the utility associated with pre-progressed disease during their remaining time in the model. The committee was not presented with any evidence that people who are alive and on treatment 5 years after starting treatment remain progression-free until they die. The company did not consider it plausible that progression-free survival would be longer than overall survival, and conducted a scenario analysis. In this, it continued to use fractional polynomial modelling for overall survival across the entire time horizon as in the revised base case. For progression-free survival, it used parametric modelling using the log-normal distribution during both the trial follow-up and extrapolation periods. The committee recalled that the log-normal distribution did not fit the data for the individual treatments

well (see [section 4.10](#)). Because of this, the committee did not consider this analysis further. It recognised the uncertainties in the company's revised base case with respect to the modelling of nivolumab, but concluded it could use it for decision-making.

- 4.19 The committee noted that the company presented a further scenario analysis that, as in the previous scenario (see [section 4.18](#)), used the log-normal distribution to model progression-free survival across the entire time horizon. However, it differed in that of those who were alive 5 years after starting treatment and still having nivolumab, the company assumed that half had the same mortality as the age-matched general population. The committee recalled that using the log-normal distribution to model progression-free survival did not produce robust estimates (see [section 4.18](#)). Furthermore, the committee noted that this scenario had little impact on the mean overall survival associated with nivolumab, which it did not expect. The company suggested that this may have been because the risk of death estimated by the log-normal curve was similar to that of the general population. The committee recalled from the NICE technology appraisal on [nivolumab](#) that the committee preferred to base its decision on a mixed model that relied 50% on a single generalised gamma model and 50% on a model that assumed a greater long-term survival benefit than in the single generalised gamma model for nivolumab. The committee concluded that the scenario analysis was unrealistic, but appreciated that the company had explored predictions of better survival for nivolumab.

Utility values

- 4.20 The committee was aware that METEOR collected health-related quality-of-life data using the EQ-5D-5L measure, which the company adjusted for age, as requested by the committee, and used in its revised base case. The committee considered these data, together with data from other studies, including those used in previous appraisals of renal cell carcinoma. It noted that the available utility values varied widely, particularly those used for the post-progression state. The ERG explained that the utility values collected from METEOR were higher than those clinicians would expect to see in clinical practice and, notably, the utility value before disease progression was higher than that of the age-

matched general population. Because of this, the ERG explored using utility values from the AXIS trial. The committee accepted that the new, more detailed version of the EQ-5D (EQ-5D-5L) used in METEOR could explain the relatively high utility values reported in this trial. It also heard from the company that there was evidence showing that utility estimates were higher using EQ-5D-5L. Another possible explanation was greater attrition bias in METEOR, in which unhealthy people were less likely to continue filling in quality-of-life questionnaires. The committee was also aware that AXIS and METEOR differed in whether they allowed patients to switch between treatment arms, the number and type of therapies that patients took before enrolling in the trial or after the disease progressed during the trial, and the prognostic scores at baseline of the study populations. In response to the second consultation, the company argued that the utility from AXIS was not the most relevant because patients in the trial had had either a cytokine or a VEGF-targeted therapy, and it was unclear what the effect was of having previous cytokines on the patient's health. The committee generally preferred sourcing utility and effectiveness from the same trial. However, it agreed that some of the utility values from METEOR appeared high, particularly the utility value before disease progression. The committee concluded that it would take into account both sets of utility values in its decision-making.

Analyses used for decision-making

4.21 The committee considered the cost-effectiveness results incorporating the revisions to the models in response to the first consultation, the new data from METEOR (cut-off of October 2016), and the confidential discounts for all technologies applied by the ERG. It was presented with results with and without everolimus included in the analysis but, because the committee concluded that everolimus was not a relevant comparator for cabozantinib, it considered only the analyses excluding everolimus. In its consideration of the cost-effectiveness estimates, the committee took into account:

- the company's revised base case (see [section 4.10](#))
- the company's scenario analysis using fractional polynomial modelling during

the trial follow-up period, and parametric modelling using the log-normal distribution during the extrapolation period (see [section 4.16](#))

- the ERG's revised base case (which reflected minor changes with minimal impact on the results compared with the company's revised base case)
- the ERG's scenario analysis exploring utility values from AXIS.

End-of-life considerations

- 4.22 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](#).
- 4.23 The committee considered the life expectancy of people with previously treated advanced renal cell carcinoma having each of the 2 comparator treatments, axitinib or nivolumab (see [section 4.3](#)). The committee noted that the mean life expectancy, based on the revised model in response to the first consultation, and the updated dataset from METEOR, was about 24 months among people with advanced renal cell carcinoma having axitinib, but not among those having nivolumab.
- 4.24 The committee discussed whether cabozantinib extended life by at least 3 months. It agreed that the results of the cost-effectiveness analyses (see [section 4.21](#)) suggested that cabozantinib was likely to extend mean overall survival by more than 3 months compared with axitinib, but not compared with nivolumab. The committee therefore concluded that cabozantinib met the end-of-life criteria when compared with axitinib, but did not meet the end-of-life criteria when compared with nivolumab.

Results of cost-effectiveness analyses

- 4.25 The committee noted that, excluding everolimus as a comparator, in the revised base-case analysis, the incremental analysis showed that cabozantinib was associated with an incremental cost-effectiveness ratio (ICER) that was below £50,000 per quality-adjusted life year (QALY) gained compared with axitinib. It also noted that, in the incremental analyses, cabozantinib dominated nivolumab (that is, it was more

effective and less expensive).

4.26 The committee discussed how the remaining uncertainties in the model could affect the results. It recalled that the cost effectiveness of cabozantinib would:

- improve (that is, cabozantinib's ICER would decrease) if:
 - the long-term survival rate were higher than predicted by the model.
- worsen (that is, cabozantinib's ICER would increase) if:
 - cabozantinib had no effect or a diminishing effect over time
 - nivolumab were associated with better long-term survival than assumed in the base case
 - the utility values from AXIS better represented the quality of life of people in the NHS than the utility values from METEOR (the ICER could increase by as much as £8,000 per QALY but would still remain below £50,000 per QALY).

The committee was satisfied that the remaining uncertainties in the model were unlikely to change the results to a degree where the incremental ICER for cabozantinib from the company's revised base case would not be cost effective compared with axitinib.

4.27 The committee was aware that, in line with the population included in METEOR, the cost-effectiveness analysis related mostly to people who had 1 or 2 previous treatments (see [section 4.11](#)), whereas the marketing authorisation for cabozantinib does not specify the number of previous treatments. The committee discussed whether the effectiveness and cost effectiveness of cabozantinib could be generalised to people who have had 3 previous treatments. It noted that, at this point, everolimus was likely to be an option, and that cabozantinib was not cost effective compared with everolimus, with ICERs exceeding £50,000 per QALY gained. The committee was aware that, according to NICE guidance, axitinib and nivolumab may also be used as fourth-line treatments. It recalled that cabozantinib would be expected to work similarly after 1 previous treatment and after 2 previous treatments, and that it would

also work after other TKIs had failed (see [section 4.5](#)). It considered that it was plausible that cabozantinib would also work similarly after 3 previous treatments. The committee acknowledged that some people in the NHS will likely have had everolimus second- or third-line, and if they remain fit for fourth-line treatment, have limited options available. Taking account of these reasons, and even though cabozantinib is not cost effective compared with everolimus, the committee agreed to keep options for this small and likely diminishing group by extending its recommendations to people who have had more than 2 previous treatments. The committee concluded that cabozantinib could be considered a cost-effective use of NHS resources for treating advanced renal cell carcinoma in adults after VEGF-targeted therapy.

Innovation

4.28 The committee considered whether cabozantinib was an innovative treatment. It heard from the clinical experts that, because of its multi-targeted approach, cabozantinib would likely have additional benefits for some patients and so could be considered innovative. The committee also heard that cabozantinib would be highly valued in patients whose disease is resistant to standard TKIs and may or may not have responded to nivolumab. The committee agreed that cabozantinib could fulfil the unmet need in these patients. However, it did not consider cabozantinib to reflect a 'step change' in treatment nor did it identify a benefit to utility that was not otherwise accounted for in the modelling.

Pharmaceutical Price Regulation Scheme (PPRS) 2014

4.29 The committee was aware of NICE's position statement on the Pharmaceutical Price Regulation Scheme (PPRS) 2014, and in particular the PPRS payment mechanism. It accepted the conclusion 'that the 2014 PPRS payment mechanism should not, as a matter of course, be regarded as a relevant consideration in its assessment of the cost effectiveness of branded medicines'. The committee heard nothing to suggest that there is any basis for taking a different view about the relevance of the PPRS to this appraisal. It therefore concluded that the

PPRS payment mechanism was not relevant in considering the cost effectiveness of the technology in this appraisal.

Summary of appraisal committee's key conclusions

TA463	Appraisal title: Cabozantinib for previously treated advanced renal cell carcinoma	Section
Key conclusion		
Cabozantinib is recommended within its marketing authorisation for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF)-targeted therapy.		1.1
In the intention-to-treat population of METEOR, progression-free and overall survival were statistically significantly improved with cabozantinib compared with everolimus.		4.8
The committee concluded that the company's simplified network reduced the potential bias associated with using immature data from TARGET. The committee was satisfied that the company's revised modelling of progression-free and overall survival was more appropriate than the original parametric modelling. The committee noted that, excluding everolimus as a comparator, in the revised base-case analysis, the incremental analysis showed that cabozantinib was associated with an incremental cost-effectiveness ratio (ICER) that was below £50,000 per quality-adjusted life year (QALY) gained compared with axitinib. It also noted that, in the incremental analyses, cabozantinib dominated nivolumab.		4.9, 4.10, 4.25
Current practice		
Clinical need of patients, including the availability of alternative treatments	The committee was aware that there remained an unmet clinical need for some people with advanced renal cell carcinoma.	4.1

	Most people fit enough for second-line treatment are offered <u>axitinib</u> , <u>nivolumab</u> or <u>everolimus</u> . If the disease progresses further, people who previously had axitinib may have nivolumab or everolimus as a third-line treatment; people who had nivolumab may have axitinib or everolimus; and people who had everolimus may have axitinib or nivolumab. The committee was aware that some patients have fourth-line treatment and beyond, but that there is no accepted treatment pathway at this point.	4.2
The technology		
Proposed benefits of the technology	The clinical experts perceived cabozantinib to be more effective than everolimus and axitinib, although it caused more adverse effects.	4.1
How innovative is the technology in its potential to make a significant and substantial impact on health-related benefits?	The committee heard from the clinical experts that, because of its multi-targeted approach, cabozantinib could be considered innovative. The committee also heard that cabozantinib would be highly valued in patients whose disease is resistant to standard tyrosine kinase inhibitors and whose disease may or may not have responded to nivolumab.	4.28
What is the position of the treatment in the pathway of care for the condition?	Cabozantinib can be used in people who have had 1 or 2 previous treatments.	4.4
Adverse reactions	The most common serious adverse reactions associated with cabozantinib are abdominal pain (3%), pleural effusion (3%), diarrhoea (2%) and nausea (2%).	2
Evidence for clinical effectiveness		

Availability, nature and quality of evidence	The main evidence came from METEOR, an open-label randomised controlled trial comparing cabozantinib with everolimus. The committee appreciated that the trial did not allow patients to switch from placebo to cabozantinib at disease progression.	4.6
	The company presented updated survival data from the METEOR trial during the first consultation (based on a cut-off date of October 2016 compared with December 2015 for the original data cut).	4.8
Relevance to general clinical practice in the NHS	The committee heard from the clinical experts that the results of METEOR were generalisable to the NHS.	4.6
Uncertainties generated by the evidence	The committee noted that the company used fractional polynomial modelling to fit survival curves. The new method used a family of related survival curves for all the treatments. However, it was a more flexible family, which improved the curve fits to the Kaplan–Meier data on overall and progression-free survival for all treatments in the network compared with the original network meta-analysis.	4.10
Are there any clinically relevant subgroups for which there is evidence of differential effectiveness?	The committee concluded that it would consider cabozantinib for the population comprising people who have had 1 or 2 previous treatments as a whole.	4.5

Estimate of the size of the clinical effectiveness including strength of supporting evidence	In the intention-to-treat population of METEOR, progression-free and overall survival were statistically significantly improved with cabozantinib compared with everolimus.	4.8
Evidence for cost effectiveness		
Availability and nature of evidence	The company used a 3-stage, partitioned-survival economic model, which the committee considered appropriate to capture the natural history of the disease.	4.11
Uncertainties around and plausibility of assumptions and inputs in the economic model	The committee concluded that assuming the effect of cabozantinib continues for up to 30 years, based on a trial with a median follow-up of under 2 years for overall survival, was highly uncertain.	4.17
	The committee suspected that the survival estimates from Ruiz-Morales et al. (2016) were likely to overestimate the survival of patients who have everolimus in the NHS.	4.15
	The committee recognised the uncertainties in the company's revised base case with respect to the modelling of nivolumab, but concluded it could use it for decision-making.	4.18, 4.19

<p>Incorporation of health-related quality-of-life benefits and utility values</p> <p>Have any potential significant and substantial health-related benefits been identified that were not included in the economic model, and how have they been considered?</p>	<p>The evidence review group (ERG) explained that the utility values collected from METEOR were higher than those clinicians would expect to see in clinical practice and, notably, the utility value before disease progression was higher than that of the age-matched general population. The committee concluded that it would also take into account both sets of utility values (AXIS and METEOR) in its decision-making.</p>	4.20
	<p>The committee did not identify a benefit to utility that was not otherwise accounted for in the modelling.</p>	4.28
<p>Are there specific groups of people for whom the technology is particularly cost effective?</p>	<p>No subgroup analyses were presented.</p>	–
<p>What are the key drivers of cost effectiveness?</p>	<ul style="list-style-type: none"> • the duration of the effect of cabozantinib • the prediction of long-term survival rate with the disease • the survival modelling of nivolumab 	4.26

Most likely cost-effectiveness estimate (given as an ICER)	The committee noted that, in the revised base-case analysis, excluding everolimus as a comparator, the incremental analysis showed that cabozantinib was associated with an ICER that was below £50,000 per QALY gained compared with axitinib. It also noted that, in the incremental analyses, cabozantinib dominated nivolumab (that is, it was more effective and less expensive).	4.25
Additional factors taken into account		
Patient access schemes (PPRS)	There are patient access schemes for cabozantinib, axitinib, everolimus and nivolumab. The ERG presented analyses that included the confidential discounts for all technologies.	–
End-of-life considerations	The committee concluded that cabozantinib met the end-of-life criteria when compared with axitinib and everolimus, but did not meet the end-of-life criteria when compared with nivolumab.	4.24
Equalities considerations and social value judgements	No equality issues were identified by consultees or the committee.	–

5 Implementation

- 5.1 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.
- 5.2 The Welsh Assembly Minister for Health and Social Services has 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 3 months of the guidance being published.
- 5.3 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 advanced renal cell carcinoma and the doctor responsible for their care thinks that cabozantinib is the right treatment, it should be available for use, in line with NICE's recommendations.
- 5.4 The Department of Health and Ipsen have agreed that cabozantinib 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 medical.information.uk@ipsen.com.

6 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.

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.

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.

Aminata Thiam

Technical lead

Ahmed Elsada

Technical adviser

Jeremy Powell

Project manager

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