

Cabozantinib with nivolumab for untreated advanced renal cell carcinoma

Technology appraisal guidance

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www.nice.org.uk/guidance/ta964

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 is 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.

All problems (adverse events) related to a medicine or medical device used for treatment or in a procedure should be reported to the Medicines and Healthcare products Regulatory Agency using the [Yellow Card Scheme](#).

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.

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1 Recommendations

- 1.1 Cabozantinib with nivolumab is recommended as an option for untreated advanced renal cell carcinoma in adults, only if:
- their disease is intermediate or poor risk as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria, and
 - nivolumab with ipilimumab or lenvatinib with pembrolizumab would otherwise be offered, and
 - the companies provide cabozantinib and nivolumab according to their [commercial arrangements](#).
- 1.2 This recommendation is not intended to affect treatment with cabozantinib with nivolumab 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

Untreated advanced renal cell carcinoma is treated based on risk status (favourable, intermediate and poor risk). For all risk statuses, treatment includes sunitinib, pazopanib or tivozanib. For intermediate- and poor-risk cancer, people may also be offered cabozantinib alone, nivolumab plus ipilimumab, or lenvatinib plus pembrolizumab.

Clinical trial evidence suggests that people having cabozantinib plus nivolumab live longer and have longer before their cancer gets worse than people having sunitinib. How well it works compared with sunitinib may change depending on the cancer's risk status, but this evidence is uncertain.

There are no clinical trials directly comparing cabozantinib plus nivolumab with treatments other than sunitinib. An indirect comparison suggests that people who have cabozantinib plus nivolumab have more time before their cancer gets worse than pazopanib or tivozanib. It also suggests that cabozantinib plus nivolumab works as well as nivolumab plus ipilimumab and lenvatinib plus pembrolizumab. But these results are uncertain because of the evidence and methods used in the indirect comparison.

For favourable-risk cancer, the cost-effectiveness estimates are above what NICE normally considers an acceptable use of NHS resources. For intermediate- and poor-risk cancer, the cost-effectiveness estimates are uncertain. But, the most likely estimates for cabozantinib plus nivolumab compared with lenvatinib plus pembrolizumab and nivolumab plus ipilimumab are within the range that NICE normally considers an acceptable use of NHS resources. So, cabozantinib plus nivolumab is recommended for people with intermediate- and poor-risk cancer if nivolumab plus ipilimumab or lenvatinib plus pembrolizumab would have otherwise been offered.

2 Information about cabozantinib with nivolumab

Marketing authorisation indication

- 2.1 Cabozantinib (Cabometyx, Ipsen) with nivolumab (Opdivo, Bristol Myers Squibb) is indicated for 'the first-line treatment of advanced renal cell carcinoma in adults'.

Dosage in the marketing authorisation

- 2.2 The dosage schedule is available in the [summary of product characteristics for cabozantinib](#).

Price

- 2.3 The list price of cabozantinib is £5,143.00 per 30 20-mg, 40-mg or 60-mg tablets (excluding VAT; BNF accessed September 2023). Costs may vary in different settings because of negotiated procurement discounts.
- 2.4 The list price of nivolumab is £439.00 per 10 mg vial for infusion, £1,317.00 per 120 mg vial for infusion and £2,633.00 per 240 mg vial for infusion (excluding VAT; BNF accessed September 2023). Costs may vary in different settings because of negotiated procurement discounts.
- 2.5 The companies have [commercial arrangements](#). These make cabozantinib and nivolumab available to the NHS with discounts. The size of the discounts are commercial in confidence. It is the companies' responsibility to let relevant NHS organisations know details of the discount.

3 Committee discussion

The [evaluation committee](#) considered evidence submitted by Ipsen, a review of this submission by the external assessment group (EAG), the EAG's economic model, and responses from stakeholders. See the [committee papers](#) for full details of the evidence.

This evaluation was done using [NICE's pilot pathway model approach](#). See [NICE's pathway model report on renal cell carcinoma](#) for full details.

The condition

Effect on quality of life

- 3.1 Patient experts explained that advanced renal cell carcinoma is life changing. They explained how renal cell carcinoma affects people's lives, starting from the shock and despair of initial diagnosis. It is difficult for people with renal cell carcinoma to continue with daily life even after successful treatment, because of the fear of recurrence. Patient experts said that people with advanced renal cell carcinoma are frequently hospitalised, may have to take early retirement and have uncertainty about the future. Commonly there is a significant psychological impact. Patient experts explained that current treatment options are associated with toxicity, which can result in needing to take time off work. There is inconsistency in which treatment options are available across the country, and for some people there are no treatment options at all. Patient experts feel there is a need for more treatment options and support. The committee understood that advanced renal cell carcinoma substantially affects people's quality of life.

Clinical management

Comparators

- 3.2 Treatment decisions for advanced renal cell carcinoma are often guided by risk status. Renal cell carcinoma is usually grouped into 2 categories: favourable-risk,

or intermediate- and poor-risk disease, as defined by the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria. All-risk includes all these risk statuses. Treatments for all risk groups include sunitinib, pazopanib, tivozanib or avelumab plus axitinib (only available through the Cancer Drugs Fund). For intermediate- or poor-risk cancer, nivolumab plus ipilimumab, lenvatinib plus pembrolizumab, or cabozantinib are also available. All treatments recommended for routine commissioning were included as comparators. Avelumab plus axitinib was not considered to be a relevant comparator because it is only available through the Cancer Drugs Fund. Clinical expert opinion confirmed that these treatments are all used at first line for untreated advanced renal cell carcinoma. The NHS England clinical lead for the Cancer Drugs Fund (from here, the Cancer Drugs Fund lead) explained that the renal cell carcinoma treatment pathway changes all the time. Currently about 500 people per year have nivolumab plus ipilimumab, and about 600 people per year have lenvatinib plus pembrolizumab. They explained that people also have sunitinib, pazopanib, tivozanib and cabozantinib. Clinical experts explained that, if recommended, cabozantinib plus nivolumab would likely displace nivolumab plus ipilimumab and lenvatinib plus pembrolizumab. Clinical experts and the Cancer Drugs Fund lead explained that combination treatments were the most appropriate comparators because they are most likely to be replaced by cabozantinib plus nivolumab. The committee concluded that in the all-risk and favourable-risk group, comparators are limited to sunitinib, pazopanib or tivozanib. But, the most appropriate comparators for the intermediate- or poor-risk subgroup were likely to be nivolumab plus ipilimumab and lenvatinib plus pembrolizumab.

Clinical effectiveness

CheckMate 9ER

- 3.3 The main source of evidence for cabozantinib plus nivolumab for renal cell carcinoma was CheckMate 9ER, a single-blind randomised controlled trial comparing cabozantinib plus nivolumab with sunitinib. There were 651 people from all risk groups enrolled in the trial, which had a final median follow up of 44 months. Cabozantinib plus nivolumab had a median overall survival of 49.5 months compared with 35.5 months for sunitinib (hazard ratio 0.7 [95%

confidence interval (CI) 0.56 to 0.87]). Median progression-free survival was 16.6 months compared with 8.4 months for sunitinib (hazard ratio 0.59 [95% CI 0.49 to 0.71]). The evidence suggested that cabozantinib plus nivolumab slows progression and lengthens life for people with renal cell carcinoma when compared with sunitinib. There are no further data cuts planned for CheckMate 9ER. The committee concluded that CheckMate 9ER suggests that cabozantinib plus nivolumab is clinically effective compared with sunitinib when assessed across all risk groups.

Differences between subgroups

- 3.4 The EAG explained there may be differences in cabozantinib plus nivolumab's effectiveness compared with sunitinib in the favourable-risk or intermediate- and poor-risk subgroups. CheckMate 9ER stratified people by risk score. About three quarters were in the intermediate- and poor-risk subgroup and one quarter in the favourable-risk subgroup. Clinical experts explained that about 80% of people with renal cell carcinoma in the UK have intermediate- or poor-risk cancer, and that this distribution is also seen globally. For the favourable-risk subgroup, median overall survival had not been reached with cabozantinib plus nivolumab and was 47.6 months for sunitinib (hazard ratio 1.07 [95% CI 0.63 to 1.79]). Median progression-free survival was 21.4 months for cabozantinib plus nivolumab compared with 13.9 months for sunitinib (hazard ratio 0.72 [95% CI 0.49 to 1.05]). When considering the intermediate- and poor-risk subgroup, cabozantinib plus nivolumab had a median overall survival of 49.5 months compared with 29.2 months for sunitinib (hazard ratio 0.65 [95% CI 0.51 to 0.83]) and a median progression-free survival of 15.6 months compared with 7.1 months for sunitinib (hazard ratio 0.56 [95% CI 0.46 to 0.69]). The committee discussed how, while the effect was numerically better in the intermediate- and poor-risk subgroup compared with the favourable-risk subgroup, these differences were not conclusive. The company explained that, while cabozantinib plus nivolumab appears to have a different relative effect in the different subgroups, the trial was not powered to detect a statistical difference between the treatments in the subgroups. So, any comparison of treatment effects across subgroups should be interpreted with caution. The committee explained that some other clinical trials for renal cell carcinoma have also shown numerical differences in treatment effect between risk subgroups. It also explained how risk subgroups have been

considered in previous NICE recommendations and how the treatment pathway differs by risk subgroup, with different treatments available dependent on risk status. The committee concluded that cabozantinib plus nivolumab appears to slow progression compared with sunitinib in both the favourable-risk subgroup and the intermediate- and poor-risk subgroup. The committee noted that, even if a treatment has the same relative effect across risk groups, the overall benefit might be different between risk groups because of a different underlying prognosis. The committee thought there was no compelling evidence that the relative treatment effect was different in different risk groups. It concluded that, in general, investigating subgroups by risk status was appropriate, and necessary, to compare cabozantinib plus nivolumab with the most appropriate comparators and account for underlying differences between subgroups.

Cost-effectiveness estimates

Economic model

- 3.5 The committee considered the EAG's modelling approach. It concluded that the overall approach was appropriate and could be used for decision making. Full details of the economic model and the company and committee preferred assumptions are presented in [NICE's renal cell carcinoma pathway model report](#).

Committee preferred assumptions

- 3.6 The committee's preferred assumptions included:
- a state transition model considering 4 lines of treatment followed by best supportive care
 - UK real-world evidence used to inform the underlying risk and safety associated with having renal cell carcinoma and having treatment
 - using network meta-analyses to compare cabozantinib plus nivolumab to other treatments for renal cell carcinoma

- network meta-analyses applied to the baseline risk to calculate the effectiveness and safety of other treatments in the pathway
- using time-varying hazards using a fractional polynomial network meta-analysis to calculate the effectiveness of all treatments at first line, including cabozantinib plus nivolumab
- assumptions that some outcomes could be used as surrogates for other outcomes, such as progression-free survival for time to stopping treatment or time to next treatment, or vice versa
- applying published utility values previously accepted in NICE technology appraisals to capture patient health-related quality of life as their disease progresses and they have multiple lines of treatment.

Company preferred assumptions

3.7 The company explained where its preferred analysis differed from the committee's. The company preferred:

- the model to only consider 2 lines of treatment followed by best supportive care, instead of 4 lines
- using a proportional hazards network meta-analysis to calculate the effectiveness of all treatments at first line, including cabozantinib plus nivolumab, instead of the time-varying hazard fractional polynomial approach
- an assumption that time to stopping treatment be equal to progression-free survival, instead of using time to stopping treatment data from the UK real-world evidence
- using safety data from individual trials and performing a naive comparison, instead of the indirect treatment approach.

Severity modifier

3.8 The committee considered the severity of the condition (the future health lost by

people living with the condition and having standard care in the NHS). The committee may apply a greater weight to quality-adjusted life years (QALYs) if technologies are indicated for conditions with a high degree of severity (a severity modifier). The committee considered absolute and proportional QALY shortfall estimates in line with [NICE's manual on health technology evaluation](#). It noted that the severity of the condition depends on which treatment is considered standard care, and there are a range of treatments recommended for untreated advanced renal cell carcinoma. The committee was presented with 3 options for assessing whether a severity weighting applied. These were fully incremental analyses, pairwise analyses (in which the most appropriate comparator was defined), and a weighted market share approach. For the pairwise comparison, the committee considered the most appropriate comparators to be the other combination treatments of nivolumab plus ipilimumab and lenvatinib plus pembrolizumab in the intermediate- or poor-risk subgroup. The committee noted that the absolute or proportionate QALY shortfall thresholds were unlikely to be met using any of the 3 options, or when considering the most appropriate comparators in each risk group, so a severity modifier was not applied.

Acceptable ICER

- 3.9 Because of confidential commercial arrangements for cabozantinib, nivolumab, and other comparators, the cost-effectiveness results cannot be reported here. The committee considered the cost-effectiveness results when using the EAG base case and company preferred assumptions. The committee was also presented with a range of scenarios investigating the impact of different assumptions. When considering the all-risk group or favourable-risk subgroup, the cost-effectiveness estimates for cabozantinib plus nivolumab compared with available treatments were above what NICE normally considers an acceptable use of NHS resources in both the EAG's and company's base cases. When considering the intermediate- and poor-risk subgroup, the committee agreed that cabozantinib plus nivolumab would have to represent good value for money compared with both nivolumab plus ipilimumab and lenvatinib plus pembrolizumab to be recommended. This is because these treatments could be displaced by cabozantinib plus nivolumab and [NICE's technology appraisal guidance on lenvatinib with pembrolizumab for untreated advanced RCC](#)

specifies that it should only be offered if nivolumab plus ipilimumab would otherwise be offered. When compared with lenvatinib plus pembrolizumab, the committee concluded that cost-effectiveness estimates for cabozantinib plus nivolumab were within the range that NICE considers an acceptable use of NHS resources. When compared with nivolumab plus ipilimumab, base-case cost-effectiveness results were above the range normally considered acceptable. The EAG explained this could be because using progression-free survival in the state transition model likely underestimated survival outcomes for nivolumab plus ipilimumab. The committee considered a key scenario where time to next treatment for nivolumab plus ipilimumab was considered to estimate the effectiveness of nivolumab plus ipilimumab. This was because of the potentially poor surrogacy between progression-free survival and overall survival seen for nivolumab plus ipilimumab. In this scenario, cost-effectiveness estimates for cabozantinib plus nivolumab compared with nivolumab plus ipilimumab were within the range that NICE considers an acceptable use of NHS resources. The committee also considered a partitioned survival analysis to investigate the interaction between nivolumab plus ipilimumab outcomes and any impact on cost effectiveness. In this scenario, outcomes for nivolumab plus ipilimumab were similar to cabozantinib plus nivolumab. The committee still preferred a state transition modelling approach but highlighted that it was useful to consider alternative model structures to investigate the relationship between overall survival and progression-free survival, especially for instances where surrogacy relationships break down. The committee thought that the true effectiveness of nivolumab plus ipilimumab was likely to be somewhere between the base case and the key time to next treatment scenario. The committee concluded that cabozantinib plus nivolumab was likely to offer good value for money when compared with both nivolumab plus ipilimumab and lenvatinib plus pembrolizumab. So, cabozantinib plus nivolumab is recommended for people with untreated intermediate- or poor-risk renal cell carcinoma who would have otherwise been offered nivolumab plus ipilimumab or lenvatinib plus pembrolizumab.

Other factors

Equality

- 3.10 The committee heard that some people may have difficulty accessing healthcare or rely on carers to assist them, so may struggle to travel to hospital for regular infusions. The committee commented that these are not equality issues that can be addressed by NICE technology appraisal recommendations. However, the committee considered that it had not seen any information indicating that cabozantinib plus nivolumab would increase access to treatment. The committee did not identify any other equality issues.

Innovation

- 3.11 The committee considered if cabozantinib plus nivolumab was innovative. The committee saw no evidence that cabozantinib plus nivolumab lessened the psychological impact of renal cell carcinoma more than other available treatments, so expected this to be captured in the economic modelling. It did not identify additional benefits of cabozantinib plus nivolumab not captured in the economic modelling. The committee concluded that the benefits of cabozantinib plus nivolumab were taken into account in the cost-effectiveness results.

Conclusion

Recommendation

- 3.12 The committee concluded that cabozantinib plus nivolumab is an effective treatment for renal cell carcinoma. The committee heard from patients and clinical experts that further treatment options would be appreciated. The most plausible cost-effectiveness estimates for all- and favourable-risk cancer were above what NICE considers an acceptable use of NHS resources for all comparators. But, when considering the most appropriate comparators for intermediate- and poor-risk cancer (nivolumab plus ipilimumab and lenvatinib

plus pembrolizumab), the most plausible cost-effectiveness estimates were within what NICE considers acceptable. So, cabozantinib plus nivolumab is recommended for untreated advanced intermediate- or poor-risk renal cell carcinoma in adults when nivolumab plus ipilimumab or lenvatinib plus pembrolizumab would otherwise be offered.

4 Implementation

- 4.1 Section 7 of the [National Institute for Health and Care Excellence \(Constitution and Functions\)](#) and the [Health and Social Care Information Centre \(Functions\) Regulations 2013](#) requires integrated care boards, NHS England and, with respect to their public health functions, local authorities to comply with the recommendations in this evaluation within 3 months of its date of publication.
- 4.2 Chapter 2 of [Appraisal and funding of cancer drugs from July 2016 \(including the new Cancer Drugs Fund\) – A new deal for patients, taxpayers and industry](#) states that for those drugs with a draft recommendation for routine commissioning, interim funding will be available (from the overall Cancer Drugs Fund budget) from the point of marketing authorisation, or from release of positive draft guidance, whichever is later. Interim funding will end 90 days after positive final guidance is published (or 30 days in the case of drugs with an Early Access to Medicines Scheme designation or cost comparison evaluation), at which point funding will switch to routine commissioning budgets. The [NHS England Cancer Drugs Fund list](#) provides up-to-date information on all cancer treatments recommended by NICE since 2016. This includes whether they have received a marketing authorisation and been launched in the UK.
- 4.3 The Welsh ministers have issued directions to the NHS in Wales on implementing NICE technology appraisal guidance. When a NICE technology appraisal guidance 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 draft guidance.
- 4.4 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 renal cell carcinoma and the doctor responsible for their care thinks that cabozantinib with nivolumab is the right treatment, it should be available for use, in line with NICE's recommendations.

5 Evaluation committee members and NICE project team

Evaluation committee members

The 4 technology appraisal committees are standing advisory committees of NICE. This topic was considered by [committee B](#). Committee members from [committee A](#), [committee C](#) and [committee D](#) also took part in the meeting.

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

The [minutes of each evaluation committee meeting](#), which include the names of the members who attended and their declarations of interests, are posted on the NICE website.

Chair

Charles Crawley

Chair, technology appraisal committee B

NICE project team

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

Lewis Ralph

Technical lead

Christian Griffiths

Technical adviser

Jeremy Powell

Project manager

Update information

May 2024: this guidance was updated to add the implementation section.

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Accreditation

