NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Draft guidance consultation

Cabozantinib with nivolumab for untreated advanced renal cell carcinoma

The Department of Health and Social Care has asked the National Institute for Health and Care Excellence (NICE) to produce guidance on using cabozantinib with nivolumab in the NHS in England. The evaluation committee has considered the evidence submitted by the company and the views of non-company stakeholders, clinical experts and patient experts.

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

The evaluation committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

Issue date: November 2023

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

After consultation:

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- After considering these comments, the committee will prepare the final draft guidance.
- Subject to any appeal by stakeholders, the final draft guidance may be used as the basis for NICE's guidance on using cabozantinib with nivolumab in the NHS in England.

For further details, see NICE's manual on health technology evaluation.

The key dates for this evaluation are:

- Closing date for comments: 21 December 2023
- Second evaluation committee meeting: 1 February 2024
- Details of the evaluation committee are given in section 4

1 Recommendations

1.1 Cabozantinib plus nivolumab is not recommended, within its marketing authorisation, for untreated advanced renal cell carcinoma in adults.

1.2 This recommendation is not intended to affect treatment with cabozantinib plus 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 pembrolizumab plus lenvatinib.

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 the evidence of this is uncertain.

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

Because of limitations with the clinical evidence, the cost-effectiveness estimates are uncertain. For favourable-risk cancer, the cost-effectiveness estimates are above

what NICE normally considers a cost-effective use of NHS resources. For intermediate- and poor-risk cancer it was not possible to determine a reliable estimate. More analysis and validation is needed for the comparisons of cabozantinib plus nivolumab with pembrolizumab plus lenvatinib and nivolumab plus ipilimumab. So, cabozantinib with nivolumab is not recommended.

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, which would have also applied to this indication if cabozantinib plus nivolumab had been recommended. 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 draft 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, 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 or tivozanib. For intermediate- or poor-risk cancer, cabozantinib, nivolumab plus ipilimumab, pembrolizumab plus lenvatinib or avelumab plus axitinib (only available through the Cancer Drugs Fund) 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 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 pembrolizumab plus lenvatinib. 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 pembrolizumab plus lenvatinib. 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 pembrolizumab plus lenvatinib.

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 49.48 months compared with 35.52 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 reiterated that cabozantinib plus nivolumab is best assessed in an all-risk population. 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. The committee explained that another analysis applying the all-risk effect to each risk subgroup might reduce uncertainty. The committee 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 with some additional analyses. Full details economic model, 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
- an indirect comparison was used to compare 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 with 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
- applying 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 their preferred analysis differed from the committees. 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 pembrolizumab plus lenvatinib 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 consider a cost-effective use of NHS resources in both the EAG's and company's base cases. When considering the intermediate- and poor-risk subgroup, the committee concluded that none of the analyses reflected its preferences so it could not make a recommendation. The committee agreed that, to recommend cabozantinib plus nivolumab, it would have to represent good value for money compared with both nivolumab plus ipilimumab and pembrolizumab plus lenvatinib. This is because NICE's technology appraisal guidance on pembrolizumab with lenvatinib for untreated advanced RCC specifies that it should only be offered if they would otherwise have offered nivolumab plus ipilimumab. The committee would have preferred to see an indirect treatment comparison including updated intermediate- and poor-risk progression-free survival data for pembrolizumab plus lenvatinib. If this is not available, the committee would prefer to see alternative methods used to include pembrolizumab plus lenvatinib in the indirect treatment comparison. The committee would also like to see further scenarios and additional data to help explore and validate the modelled results for nivolumab plus ipilimumab.

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. But the analyses either showed that cabozantinib plus nivolumab was not cost effective, or did not reflect the committee's preferred assumptions, when compared with the most appropriate comparators in each risk group. So, cabozantinib plus nivolumab is not recommended for untreated advanced renal cell carcinoma in adults.

4 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

Dr 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

Hannah Nicholas

Technical adviser

Jeremy Powell

Project manager

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