NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with cabozantinib for untreated advanced or metastatic renal cell carcinoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of nivolumab in combination with cabozantinib within its marketing authorisation for untreated advanced or metastatic renal cell carcinoma.

Background

Renal cell carcinoma (RCC) is a cancer that usually originates in the lining of the tubules of the kidney (the smallest tubes inside the nephrons) that help filter the blood and make urine. RCC is the most common type of kidney cancer (more than 80% of the cases)[1]. There are several types of RCC. The main ones are clear cell (accounting for approximately 75% of cases)[1], papillary and chromophobe.

Early small RCC tumours are usually asymptomatic; the diagnosis of early RCC is often incidental after abdominal scans for other reasons[2]. The most common presenting symptoms of advanced RCC are blood in the urine (haematuria), a palpable mass in the flank or abdomen and abdominal pain. Other non-specific symptoms include fever, night sweats, malaise and weight loss. RCC is graded into stages I to IV. Stage III denotes disease that is locally advanced and/or has spread to regional lymph nodes. Metastatic RCC, in which the tumour has spread beyond the regional lymph nodes to other parts of the body, is defined as stage IV. Localised radical approaches including nephron-sparing surgery, radical nephrectomy and ablative therapies may be curative in people with localised tumours. However, around half of those who have surgery develop advanced disease later on.

Kidney cancer is the 7th most common cancer in the UK, accounting for 4% of all new cancer cases in 2017[3]. It accounts for 3% of all new female cancer cases and 4% of all new male cancer cases[3]. In 2017, 10,759 new kidney cancer cases were diagnosed in England[3]. This would equate to approximately 8,607 new cases of RCC in England in 2017. Approximately 44% of people diagnosed with kidney cancer with a known stage in England and Northern Ireland have stage III or IV disease[3]. The 5-year relative survival rate ranges from approximately 86-88% at stage I to 12-13% at stage IV for patients diagnosed with kidney cancer[4].

In patients with metastatic kidney cancer who are otherwise fit, tumour nephrectomy, combined with interferon-alfa (IFN-a) may be given. Immunotherapy, such as IFN-a or interleukin-2 (ILN-2) can be given to selected patients with “clear cell” subtype[5]. NICE technology appraisal guidance 169 recommends sunitinib as a first-line treatment option for people with advanced and/or metastatic renal cell carcinoma who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. NICE technology appraisal guidance 215 recommends pazopanib as a first-line treatment option for people with advanced renal cell carcinoma who have not received prior cytokine therapy and have an

Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. NICE technology appraisal guidance 512 recommends tivozanib for treating advanced RCC in adults who have had no previous treatment. NICE technology appraisal guidance 542 recommends cabozantinib for untreated advanced RCC that is intermediate or poor risk as defined in the International Metastatic RCC Database Consortium criteria. NICE technology appraisal guidance 581 recommends nivolumab with ipilimumab for use within the Cancer Drugs Fund as an option for adults with untreated advanced RCC that is intermediate or poor risk as defined in the International Metastatic RCC Database Consortium criteria.

The technology

Nivolumab (Opdivo, Bristol-Myers Squibb Pharmaceuticals) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. It is administered intravenously.

Cabozantinib (Cabometyx, Ispen) is a small molecule that inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. It is administered orally.

Nivolumab currently has a marketing authorisation in the UK for a number of indications, including:

- advanced RCC after prior therapy in adults
- in combination with ipilimumab as a first-line treatment of adult patients with intermediate/ poor-risk advanced RCC.

Cabozantinib currently has a marketing authorisation in the UK for the following indications:

- treatment-naïve adults with intermediate or poor risk advanced RCC
- in adults with advanced RCC following prior vascular endothelial growth factor (VEGF)-targeted therapy.

Nivolumab in combination with cabozantinib does not currently have a marketing authorisation in the UK for untreated advanced or metastatic RCC. Nivolumab with cabozantinib has been studied in a clinical trial, compared with sunitinib, in adults with untreated, advanced or metastatic RCC.

Intervention(s)	Nivolumab in combination with cabozantinib
Population(s)	People with untreated advanced or metastatic renal cell carcinoma
Comparators	• Pazopanib • Tivozanib • Sunitinib • Cabozantinib

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. If the technology is likely to provide similar or greater health benefits at similar or lower cost than technologies recommended in published NICE technology appraisal guidance for the same indication, a cost-comparison may be carried out. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention, comparator and subsequent treatment technologies will be taken into account.
Other considerations	Guidance will only be issued in accordance with the marketing authorisation. Where the wording of the therapeutic indication does not include specific treatment combinations, guidance will be issued only in the context of the evidence that has underpinned the marketing authorisation granted by the regulator.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals:** Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (2019) NICE technology appraisal guidance 581 Tivozanib for treating renal cell carcinoma (2018) NICE technology appraisal guidance 512 Cabozantinib for untreated advanced renal cell carcinoma (2018) NICE technology appraisal guidance 542 Pazopanib for the first-line treatment of advanced renal cell carcinoma (2011, updated 2013) NICE technology appraisal guidance 215. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (2009, updated 2017) NICE

	technology appraisal guidance 169. Bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for the treatment of advanced and/or metastatic renal cell carcinoma (2009, updated 2017) NICE technology appraisal guidance 178 **Appraisals in development:** Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma NICE technology appraisal guidance. Publication expected April 2020. Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma NICE technology appraisal guidance. Publication expected TBC. Appraisal consultation ends 4th March 2020. **Related guidelines:** Suspected cancer: recognition and referral (2015 updated 2017) NICE guideline NG12 Improving outcomes in urological cancers (2002) Cancer service guideline CSG2 **Related NICE Pathways:** Renal cancer (2017) NICE pathway
Related National Policy	NHS England (2019) The NHS long term plan NHS England (2019) Specialised kidney, bladder and prostate cancer services (Adults). Service specification. Reference: 170114S NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 15 adult specialist renal services. Chapter 105 specialist cancer services (adults). Department of Health (April 2016) NHS Outcomes Framework 2016-2017: Domain 1. Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 Department of Health (2014) The national cancer strategy: 4th annual report NHS England (2013) 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). Service specification. Ref: B01/S/a.

Questions for consultation

Have all relevant comparators for nivolumab with cabozantinib been included in the scope? In clinical practice, would use of any comparators differ by ECOG performance status? In clinical practice, would use of any comparators differ by the International Metastatic RCC Database Consortium criteria? Which treatments are considered to be established clinical practice in the NHS for untreated advanced or metastatic renal cell carcinoma?

Are the outcomes listed appropriate?

Are there any subgroups of people in whom nivolumab with cabozantinib is expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider nivolumab in combination with cabozantinib will fit into the existing NICE pathway, Renal cancer (2017)?

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the proposed remit and scope may need changing in order to meet these aims. In particular, please tell us if the proposed remit and scope:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which nivolumab with cabozantinib are licensed;

- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;

- could have any adverse impact on people with a particular disability or disabilities.

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts.

Do you consider nivolumab with cabozantinib to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?

Do you consider that the use of nivolumab with cabozantinib can result in any potential significant and substantial health-related benefits that are unlikely to be included in the QALY calculation?

Please identify the nature of the data which you understand to be available to enable the Appraisal Committee to take account of these benefits.

To help NICE prioritise topics for additional adoption support, do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.

NICE intends to appraise this technology through its Single Technology Appraisal (STA) Process. We welcome comments on the appropriateness of appraising this topic through this process. (Information on the Institute's Technology Appraisal processes is available at http://www.nice.org.uk/article/pmg19/chapter/1-Introduction).

NICE has published an addendum to its guide to the methods of technology appraisal (available at https://www.nice.org.uk/Media/Default/About/what-we-do/NICE-guidance/NICE-technology-appraisals/methods-guide-addendum-cost-comparison.pdf), which states the methods to be used where a cost comparison case is made.

- Would it be appropriate to use the cost comparison methodology for this topic?
- Is the new technology likely to be similar in its clinical efficacy and resource use to any of the comparators?
- Is the primary outcome that was measured in the trial or used to drive the model for the comparator(s) still clinically relevant?
- Is there any substantial new evidence for the comparator technology/ies that has not been considered? Are there any important ongoing trials reporting in the next year?

References

1 Cancer Research UK (2020). Types of kidney cancer. Accessed February 2020.

2 Petejova N, Martinek A. Renal cell carcinoma: Review of etiology, pathophysiology and risk factors. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2016 Jun;160(2):183-94. Available from: https://doi.org/10.5507/bp.2015.050

3 Cancer Research UK (2020). Kidney cancer incidence statistics. Accessed February 2020.

4 Cancer Research UK (2019). Kidney cancer survival statistics. Accessed February 2020.

5 Patient UK (2016). Renal cancer. Accessed March 2020.

