

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Health Technology Appraisal**

**Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma  
Draft scope**

**Draft remit/appraisal objective**

To appraise the clinical and cost effectiveness of pembrolizumab with axitinib within its marketing authorisation for untreated 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)<sup>Error! Reference source not found.</sup>. There are several types of RCC. The main ones are clear cell (accounting for approximately 75% of cases), papillary and chromophobe<sup>1</sup>.

Early small RCC tumours are usually asymptomatic; the diagnosis of early RCC is often incidental after abdominal scans for other reasons. 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

In 2015, 12,547 new kidney cancer cases were diagnosed in England<sup>2</sup>. In 2015, approximately 44% of people diagnosed with kidney cancer had stage III or IV disease and 25% to 31% had metastases<sup>3</sup>. The 5-year relative survival rate ranges approximately from 83% at stage I to 6% at stage IV for patients diagnosed with RCC<sup>4</sup>.

The aim of treatment is to stop the growth of new blood vessels within the tumour. In untreated RCC, NICE has issued the following technology appraisal (TA) guidance:

- TA169 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.'

- TA215 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’.
- TA512 recommends tivozanib for treating advanced renal cell carcinoma in adults who have had no previous treatment.

**The technology**

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody (IgG4/kappa isotype with a stabilising sequence alteration in the Fc region) produced in Chinese hamster ovary cells by recombinant DNA technology. It is administered intravenously.

Axitinib (Inlyta, Pfizer) is an oral multi-targeted kinase receptor inhibitor with anti-tumour activity. Axitinib inhibits vascular endothelial growth factor receptor (VEGFR) -1, -2 and -3, platelet-derived growth factor receptor (PDGFR), and c-kit, which may result in inhibition of angiogenesis in tumours.

Pembrolizumab with axitinib does not currently have a marketing authorisation in the UK for untreated RCC. Pembrolizumab with axitinib is being studied in a clinical trial compared with sunitinib monotherapy in people with untreated advanced or metastatic RCC with clear cell component.

Pembrolizumab has a marketing authorisation in the UK for treating advanced RCC after prior therapy, and this indication has already been appraised in NICE Technology appraisal 333.

<b>Intervention(s)</b>	Pembrolizumab with axitinib
<b>Population(s)</b>	Adults with untreated metastatic renal cell carcinoma with clear cell component
<b>Comparators</b>	<ul style="list-style-type: none"> <li>• Tivozanib</li> <li>• Pazopanib</li> <li>• Sunitinib</li> <li>• Nivolumab with ipilimumab (subject to ongoing NICE appraisal)</li> <li>• Cabozantinib (subject to ongoing NICE appraisal)</li> </ul>

<b>Outcomes</b>	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> <li>• overall survival</li> <li>• progression-free survival</li> <li>• adverse effects of treatment</li> <li>• health-related quality of life.</li> </ul>
<b>Economic analysis</b>	<p>The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year.</p> <p>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.</p> <p>Costs will be considered from an NHS and Personal Social Services perspective.</p> <p>The availability of any patient access schemes for the intervention or comparator technologies will be taken into account.</p>
<b>Other considerations</b>	<p>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.</p>
<b>Related NICE recommendations and NICE Pathways</b>	<p><b>Related Technology Appraisals:</b></p> <p><a href="#">Tivozanib for treating advanced renal cell carcinoma</a> (2018) NICE technology appraisal guidance 512. Review date March 2021.</p> <p><a href="#">Pazopanib for the first-line treatment of advanced renal cell carcinoma</a> (2011 updated 2013) NICE technology appraisal guidance 215. Static list.</p> <p><a href="#">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</a> (2009) NICE technology appraisal guidance 178. Static list.</p> <p><a href="#">Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma</a> (2009) NICE technology appraisal guidance 169. Static list.</p>

	<p><b>Appraisals in development (including suspended appraisals)</b></p> <p><a href="#">Cabozantinib for untreated locally advanced or metastatic renal cell carcinoma</a> NICE technology appraisals guidance [ID1208]. Publication expected October 2018.</p> <p><a href="#">Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma</a>. NICE technology appraisals guidance [ID1182]. Publication expected October 2018.</p> <p><a href="#">Atezolizumab plus bevacizumab for untreated locally advanced or metastatic renal cell carcinoma</a>. NICE technology appraisals guidance [ID1365]. Publication date to be confirmed.</p> <p><a href="#">Renal cell carcinoma – sunitinib</a>. NICE technology appraisals guidance [ID1076]. Publication date to be confirmed.</p> <p><b>Related NICE Pathways:</b> Renal cancer (2015) NICE pathway <a href="http://pathways.nice.org.uk/pathways/renal-cancer">http://pathways.nice.org.uk/pathways/renal-cancer</a></p>
<p><b>Related National Policy</b></p>	<p>NHS England (2017) <a href="#">Manual for Prescribed Specialised Services 2017/18</a>. Section 105 <a href="https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf">https://www.england.nhs.uk/wp-content/uploads/2017/10/prescribed-specialised-services-manual-2.pdf</a></p> <p>Department of Health, NHS Outcomes Framework 2016-2017 (published 2016): Domains 1. <a href="https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017">https://www.gov.uk/government/publications/nhs-outcomes-framework-2016-to-2017</a></p> <p>Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020 <a href="http://www.cancerresearchuk.org/about-us/cancer-strategy-in-england">http://www.cancerresearchuk.org/about-us/cancer-strategy-in-england</a></p> <p>Department of Health (2014) The national cancer strategy: 4th annual report <a href="https://www.gov.uk/government/publications/the-">https://www.gov.uk/government/publications/the-</a></p>

	<p><a href="#">national-cancer-strategy-4th-annual-report</a></p> <p>NHS England (2013) B14. Cancer: Specialised kidney, bladder and prostate cancer services (Adult). NHS Standard Contract.</p> <p><a href="https://www.england.nhs.uk/wp-content/uploads/2013/06/b14-cancr-kidney-blad-pros.pdf">https://www.england.nhs.uk/wp-content/uploads/2013/06/b14-cancr-kidney-blad-pros.pdf</a></p>
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### Questions for consultation

Have all relevant comparators for pembrolizumab with axitinib been included in the scope?

Which treatments are considered to be established clinical practice in the NHS for untreated metastatic renal cell carcinoma?

Are the outcomes listed appropriate?

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

Where do you consider pembrolizumab with axitinib will fit into the existing NICE [renal cancer](#) pathway?

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 pembrolizumab with axitinib will be 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 pembrolizumab with axitinib 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 pembrolizumab with axitinib 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 [Types of kidney cancer](#). Accessed January 2017.
2. Cancer Research UK [Kidney cancer incidence](#). Accessed June 2018
3. Cancer Research UK [Kidney cancer incidence by stage at diagnosis](#). Accessed June 2018.
4. Cancer Research UK [Kidney cancer survival by stage at diagnosis](#). Accessed June 2018.