

**NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE**

**Health Technology Evaluation**

**Treatments for renal cell carcinoma**

**Final scope**

**Remit/evaluation objective**

To appraise the clinical and cost effectiveness of treatments for renal cell carcinoma (RCC).

**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, accounting for more than 80% of cases<sup>1</sup>. There are several types of RCC. The main ones are clear cell (accounting for around 75% of cases), papillary and chromophobe<sup>1</sup>.

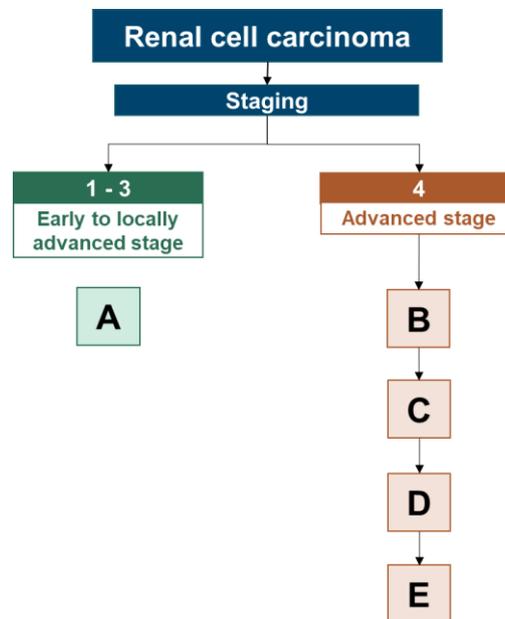
Treatment depends on the location and stage of the cancer. There are different staging systems for renal cell carcinoma, including the number system<sup>2</sup>. It looks at the number and size of kidney tumours. The number system has 4 stages:

- Stage 1 and 2 (early stage where tumour is localised to the kidney)
- Stage 3 (locally advanced stage with possible spread to regional lymph nodes)
- Stage 4 (advanced, metastatic stage where tumour has spread beyond regional lymph nodes to other parts of the body)

In 2017, 9,298 new kidney cancer cases were diagnosed in England<sup>3</sup>. Of those, 40.2% had stage 1 disease, 7.6% had stage 2 disease, 15.5% had stage 3 disease and 20.5% had stage 4 disease<sup>4</sup>.

## Treatment pathway

The treatment pathway for RCC can be divided into interconnected decision points based on the number staging system and line of therapy (Figure 1). These represent what treatments are available at each stage of the disease. (Figure 1).



**Figure 1 Treatment pathway for renal cell carcinoma**

### **A: Early stage to locally advanced stage, eligible for surgery**

Early stage RCC is localised to the kidneys. Treatment options for localised tumours include laparoscopic or open surgery (nephrectomy), which can be partial (nephron sparing) or total, and ablation techniques including radiofrequency ablation, microwave ablation, cryoablation and stereotactic body radiation therapy (SABR). These are performed with curative intent. Nephrectomy is the only treatment option for locally advanced RCC. After tumour resection, the cancer can be graded. Risk of recurrence is greater in higher-grade cancers. Pembrolizumab is recommended by NICE technology appraisal [TA830](#) for adjuvant treatment after nephrectomy to those whose cancer is at increased risk of recurrence.

### **B: Advanced, metastatic first line**

Current treatment options for untreated advanced RCC include tyrosine kinase inhibitors (TKIs). TKIs offered for untreated RCC include sunitinib, pazopanib or tivozanib as recommended by NICE technology appraisal guidance ([TA169](#), [TA215](#) and [TA512](#)). In addition, immunotherapy combinations can be offered in the first line. [TA645](#) recommends avelumab with axitinib (a PD-1/PD-L1 inhibitor with a TKI) for use within the Cancer Drugs Fund for untreated advanced RCC. For people with intermediate or poor-risk cancer as defined by the International Metastatic RCC Database Consortium (IMDC), [TA542](#) recommends cabozantinib (a TKI), [TA780](#) recommends nivolumab plus ipilimumab (a PD-1 inhibitor with a CTLA-4

inhibitor), and [TA858](#) recommends lenvatinib with pembrolizumab (a TKI with a PD-1/PD-L1 inhibitor).

### C: Advanced, metastatic second line

People whose disease has progressed on a cytokine or TKI can have axitinib as a second-line treatment ([TA333](#)). People whose disease has progressed on a VEGF-targeted therapy can have cabozantinib ([TA463](#)) or lenvatinib plus everolimus ([TA498](#)) as a second-line treatment. Nivolumab is also an option for second-line treatment ([TA417](#)) if they have not previously had a PD-1/PD-L1 inhibitor. In addition, people could have TKIs if they had not had them in the first-line setting.

### D: Advanced, metastatic third line

If the disease progresses again, people may have, as third-line treatment, whichever of axitinib ([TA333](#)), nivolumab ([TA417](#)), cabozantinib ([TA463](#)) or lenvatinib plus everolimus ([TA498](#)) as a third-line treatment if any of these treatments have not been previously used.

### E: Advanced, metastatic fourth line

Everolimus is recommended by NICE ([TA432](#)) for disease that has progressed after VEGF therapy and is mainly used in clinical practice after 3 previous treatments, that is, as a fourth-line treatment.

**Table 1: New treatments being appraised**

Decision point	B
Interventions	Cabozantinib with nivolumab (Ipsen)
Populations	People with untreated advanced or metastatic renal cell carcinoma
Comparators	<ul style="list-style-type: none"> <li>• Pazopanib</li> <li>• Tivozanib</li> <li>• Sunitinib</li> <li>• Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria)</li> <li>• Nivolumab plus ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria)</li> <li>• Lenvatinib with pembrolizumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria)</li> <li>• Active surveillance</li> </ul>
Outcomes	<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>• response rates</li> <li>• duration of response</li> </ul>

	<ul style="list-style-type: none"> <li>• time on treatment/time to next treatment</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 commercial arrangements for the intervention, comparator or subsequent treatment technologies will be taken into account.</p>
<b>Other considerations</b>	<p>If the evidence allows the following subgroup will be considered:</p> <ul style="list-style-type: none"> <li>• intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria</li> <li>• prior treatment</li> </ul> <p>Guidance will only be issued in accordance with the marketing authorisations. Where the wording of the therapeutic indications do 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</b>	<p><b>Related technology appraisals:</b></p> <p><a href="#">Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma</a> (2022) NICE technology appraisal guidance TA858</p> <p><a href="#">Pembrolizumab for adjuvant treatment of renal cell carcinoma</a> (2022) NICE technology appraisal guidance TA830</p> <p><a href="#">Nivolumab with ipilimumab for untreated advanced renal cell carcinoma</a> (2022) NICE technology appraisal guidance TA780</p> <p><a href="#">Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma</a> (2020) NICE technology appraisal guidance TA645</p>

	<p><a href="#">Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma</a> (2020) NICE technology appraisal guidance TA650</p> <p><a href="#">Tivozanib for treating renal cell carcinoma</a> (2018) NICE technology appraisal guidance TA512</p> <p><a href="#">Cabozantinib for untreated advanced renal cell carcinoma</a> (2018) NICE technology appraisal guidance TA542</p> <p><a href="#">Pazopanib for the first-line treatment of advanced renal cell carcinoma</a> (2011, updated 2013) NICE technology appraisal guidance TA215.</p> <p><a href="#">Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma</a> (2009, updated 2017) NICE technology appraisal guidance TA169.</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, updated 2017) NICE technology appraisal guidance TA178</p> <p><a href="#">Lenvatinib with everolimus for previously treated advanced renal cell carcinoma</a> (2018) NICE technology appraisal guidance TA498</p> <p><a href="#">Cabozantinib for previously treated advanced renal cell carcinoma</a> (2017) NICE technology appraisal guidance TA463</p> <p><a href="#">Nivolumab for previously treated advanced renal cell carcinoma</a> (2016) NICE technology appraisal guidance TA417</p> <p><a href="#">Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment.</a> (2015) NICE technology appraisal guidance TA333</p> <p><a href="#">Everolimus for advanced renal cell carcinoma after previous treatment</a> (2017) NICE technology appraisal guidance TA432</p> <p><b>Technology appraisals in development:</b>  <a href="#">Belzutifan for treating clear-cell renal carcinoma caused by von Hippel-Lindau disease [ID3932]</a> NICE</p>
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	<p>technology appraisal. Publication expected November 2023</p> <p><b>Related guidelines:</b>  <a href="#">Suspected cancer: recognition and referral</a> (2015 updated 2017) NICE guideline NG12  <a href="#">Improving outcomes in urological cancers</a> (2002) Cancer service guideline CSG2</p> <p><b>Related Quality Standards:</b>  <a href="#">Suspected cancer</a> (2016 updated 2017) NICE quality standard 124</p>
<p><b>Related national policy</b></p>	<p><b>NHS England:</b></p> <p>NHS England (2019) <a href="#">The NHS long term plan</a></p> <p>NHS England (2019) <a href="#">Specialised kidney, bladder and prostate cancer services (Adults)</a>. Service specification. Reference: 170114S</p> <p>NHS England (2018/2019) <a href="#">NHS manual for prescribed specialist services (2018/2019)</a>. Chapter 15 adult specialist renal services. Chapter 105 specialist cancer services (adults).</p> <p>NHS England (2013) <a href="#">2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult)</a>. Service specification. Ref: B15/S/a.</p> <p>NHS England (2013) <a href="#">2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages)</a>. Service specification. Ref: B01/S/a.</p> <p><b>Other policy documents:</b></p> <p>Department of Health (April 2016) <a href="#">NHS Outcomes Framework 2016-2017</a>: Domain 1.</p> <p>Independent Cancer Taskforce (2015) <a href="#">Achieving world-class cancer outcomes: a strategy for England 2015-2020</a></p> <p>NHS Digital (2022) <a href="#">NHS Outcomes Framework England, March 2022 Annual Publication</a></p>

### References

1. Cancer Research UK. [Kidney cancer types and grades](#). Accessed October 2022.
2. Cancer Research UK. [Number stages for kidney cancer](#). Accessed October 2022.
3. Office for National Statistics [Cancer registration statistics, England: 2017 \(April 2019\)](#). Accessed October 2022.
4. Office for National Statistics. [Cancer survival in England: adult, stage at diagnosis and childhood – patients followed up to 2018](#). Accessed 28 October 2022.