NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Evaluation

Treatments for renal cell carcinoma

Draft scope

Draft 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[1]. There are several types of RCC. The main ones are clear cell (accounting for around 75% of cases), papillary and chromophobe[1].

Treatment depends on the location and stage of the cancer. There are different staging systems for renal cell carcinoma, including the number system[2]. 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[3]. 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[4]. The 5-year survival was 86.8%, 76.6%, 74.2% and 12.4% for stage 1,2,3, and stage 4 disease, respectively[4].

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).

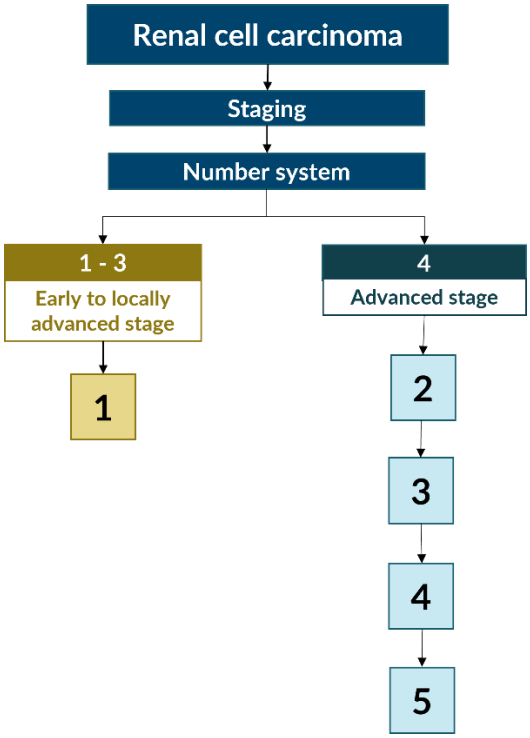

Figure 1 Treatment pathway for renal cell carcinoma

1: 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 and cryoablation. 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.

2: 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, 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. Lenvatinib with pembrolizumab (a TKI with a PD-1/PD-L1 inhibitor) is also being appraised by NICE for untreated RCC (ID3760). For people with intermediate or poor-risk

cancer as defined by the International Metastatic RCC Database Consortium (IMDC), TA542 recommends cabozantinib (a TKI), and TA780 recommends nivolumab plus ipilimumab (a PD-1 inhibitor with a CTLA-4 inhibitor).

3: Advanced, metastatic second line

People whose disease has progressed on a cytokine or tyrosine kinase inhibitor 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.

4: 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) was not used as second-line treatment.

5: 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	2	3, 4 and 5
Interventions	Cabozantinib with nivolumab (NICE Technology Appraisal ID6184, Ipsen)	Belzutifan (NICE Technology Appraisal ID6154, MSD)
Populations	People with untreated advanced or metastatic renal cell carcinoma	People with advanced renal cell carcinoma after a PD-1/PD-L1 inhibitor and a VEGF-TKI
Comparators	• Pazopanib • Tivozanib • Sunitinib • Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivolumab plus ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria)	• Cabozantinib • Axitinib • Lenvatinib plus everolimus • Everolimus • Best supportive care

	• Lenvatinib with pembrolizumab (subject to ongoing NICE evaluation)	
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. 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 or subsequent treatment technologies will be taken into account.	
Other considerations	If the evidence allows the following subgroup will be considered: • intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria • prior treatment 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.	
Related NICE recommendations	Related technology appraisals: Pembrolizumab for adjuvant treatment of renal cell carcinoma (2022) NICE technology appraisal guidance TA830 Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (2022) NICE technology appraisal guidance TA780	

	Tivozanib for treating renal cell carcinoma (2018) NICE technology appraisal guidance TA512 Cabozantinib for untreated advanced renal cell carcinoma (2018) NICE technology appraisal guidance TA542 Pazopanib for the first-line treatment of advanced renal cell carcinoma (2011, updated 2013) NICE technology appraisal guidance TA215. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (2009, updated 2017) NICE technology appraisal guidance TA169. 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 TA178 Lenvatinib with everolimus for previously treated advanced renal cell carcinoma (2018) NICE technology appraisal guidance TA498 Cabozantinib for previously treated advanced renal cell carcinoma (2017) NICE technology appraisal guidance TA463 Nivolumab for previously treated advanced renal cell carcinoma (2016) NICE technology appraisal guidance TA417 Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment. (2015) NICE technology appraisal guidance TA333 Avelumab with axitinib for untreated advanced renal cell carcinoma (2020) NICE technology appraisal guidance TA645 Everolimus for advanced renal cell carcinoma after previous treatment (2017) NICE technology appraisal guidance TA432 **Technology appraisals in development:** Atezolizumab plus bevacizumab for untreated locally advanced or metastatic renal cell carcinoma [ID1365]

	NICE technology appraisal guidance. Publication expected TBC Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547] NICE technology appraisal guidance. Publication expected TBC Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426] NICE technology appraisal guidance. Publication expected TBC. Belzutifan for treating clear-cell renal carcinoma caused by von Hippel-Lindau disease [ID3932] NICE technology appraisal. Publication expected 31 May 2023 Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma [ID3760] NICE technology appraisal. Publication expected January 2023 **Related guidelines:** Suspected cancer: recognition and referral (2015 updated 2017) NICE guideline NG12 Improving outcomes in urological cancers (2002) Cancer service guideline CSG2 **Related Quality Standards:** Suspected cancer (2016 updated 2017) NICE quality standard 124
Related national policy	**NHS England:** 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). NHS England (2013) 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). Service specification. Ref: B15/S/a.

	NHS England (2013) 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). Service specification. Ref: B01/S/a. **Other policy documents:** 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 NHS Digital (2022) NHS Outcomes Framework England, March 2022 Annual Publication

Questions for consultation

Have all relevant treatments for RCC been included in the scope? Which treatments are established clinical practice in the NHS at each point in the RCC pathway?

Does the pathway described represent current NHS clinical care? Is the pathway split appropriately into clearly defined decision problems?

Is the staging system used to define patient populations and decision points the most relevant in NHS clinical practice? Are there other staging systems that have not been considered?

Are the positions for the proposed treatments in the pathway appropriate for NHS clinical practice?

In the advanced metastatic setting, how many lines of treatment would an average person be expected to have in clinical practice? Does this vary? Are there any biological reasons for any variation?

How does what is had as first-line systemic treatment affect the second- and later-line systemic treatment?

Are there rules about using an immunotherapy in the advanced setting if one has been used in the adjuvant setting (for example, pembrolizumab), or if not currently, what do you expect these rules to be in the future?

Are there rules about using immunotherapies in sequence in the advanced setting? Or if not currently, what do you expect these rules to be in the future?

What treatments are offered in the locally advanced setting? Are they different to those offered in the advanced metastatic setting? Are treatment sequencing rules in place if a tumour metastasises?

What are the key unanswered clinical questions about sequencing of treatments within RCC? Are you aware of any trials planned to address these?

Are the outcomes listed appropriate? Have all core outcomes for RCC been considered? Have all relevant patient-reported outcomes been considered? Do outcomes differ across different points in the RCC pathway?

Are there any groups of people in whom the proposed treatments are expected to be more clinically and cost effective? Are there other groups of people who should be examined separately?

Is there any relevant real-world evidence or are there registries collecting data for people with RCC?

Would cabozantinib plus nivolumab or belzutifan be candidates for managed access?

Do you consider that the use of cabozantinib plus nivolumab or belzutifan can result in any potential 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 committee to take account of these benefits.

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

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

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.