

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Nivolumab with cabozantinib for untreated advanced or metastatic renal cell carcinoma

Final scope

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, accounting for more than 80% of cases¹. There are several types of RCC. The main ones are clear cell (around 75% of cases¹), papillary and chromophobe.

Early small RCC tumours are usually asymptomatic; the diagnosis of early RCC is often incidental after abdominal scans for other reasons². 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 categorised into stages 1 to 4. Stage 3 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 4. The International Metastatic RCC Database Consortium (IMDC) Risk Score is also widely used in clinical trials to categorise patients into favourable-, intermediate- or poor-risk based on certain criteria. 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 2017³. It accounts for 3% of all new female cancer cases and 4% of all new male cancer cases³. In 2017, 10,759 new kidney cancer cases were diagnosed in England³, equating to around 8,607 new cases of RCC. Around 44% of people diagnosed with kidney cancer with a known stage in England and Northern Ireland have stage 3 or 4 disease³. The 5-year relative survival rate ranges from around 86-88% at stage 1 to 12-13% at stage 4 for patients diagnosed with kidney cancer⁴.

[NICE technology appraisal guidance 169](#) recommends sunitinib as a first-line treatment option for people with advanced and/or metastatic RCC 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 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 IMDC 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 IMDC 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, Ipsen) 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 several indications, including:

- advanced RCC after prior therapy in adults
- in combination with ipilimumab for the treatment of adults 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 an open-label, phase 3 randomised trial in comparison 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	<ul style="list-style-type: none"> • Pazopanib • Tivozanib • Sunitinib • Cabozantinib (only for intermediate- or poor-risk

	disease as defined in the IMDC criteria)
Outcomes	<p>The outcome measures to be considered include:</p> <ul style="list-style-type: none"> • overall survival • progression-free survival • response rates • adverse effects of treatment • health-related quality of life.
Economic analysis	<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>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.</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 and subsequent treatment technologies will be taken into account.</p>
Other considerations	<p>If the evidence allows the following subgroup will be considered:</p> <ul style="list-style-type: none"> • intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria <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>
Related NICE recommendations and NICE Pathways	<p>Related Technology Appraisals:</p> <p>Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (2019) NICE technology appraisal guidance 581</p> <p>Tivozanib for treating renal cell carcinoma (2018) NICE technology appraisal guidance 512</p> <p>Cabozantinib for untreated advanced renal cell carcinoma (2018) NICE technology appraisal guidance 542</p>

	<p>Pazopanib for the first-line treatment of advanced renal cell carcinoma (2011, updated 2013) NICE technology appraisal guidance 215.</p> <p>Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (2009, updated 2017) NICE technology appraisal guidance 169.</p> <p>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</p> <p>Appraisals in development:</p> <p>Atezolizumab plus bevacizumab for untreated locally advanced or metastatic renal cell carcinoma [ID1365] NICE technology appraisal guidance. Publication expected TBC</p> <p>Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547] NICE technology appraisal guidance. Publication expected TBC</p> <p>Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426] NICE technology appraisal guidance. Publication expected TBC.</p> <p>Related guidelines:</p> <p>Suspected cancer: recognition and referral (2015 updated 2017) NICE guideline NG12</p> <p>Improving outcomes in urological cancers (2002) Cancer service guideline CSG2</p> <p>Related NICE Pathways:</p> <p>Renal cancer (2017) NICE pathway</p>
<p>Related National Policy</p>	<p>NHS England (2019) The NHS long term plan</p> <p>NHS England (2019) Specialised kidney, bladder and prostate cancer services (Adults). Service specification. Reference: 170114S</p> <p>NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019). Chapter 15 adult specialist renal services. Chapter 105 specialist cancer services (adults).</p> <p>Department of Health (April 2016) NHS Outcomes Framework 2016-2017: Domain 1.</p> <p>Independent Cancer Taskforce (2015) Achieving world-class cancer outcomes: a strategy for England 2015-2020</p>

	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.
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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.