NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Lenvatinib with everolimus or pembrolizumab for untreated advanced renal cell carcinoma

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of lenvatinib with everolimus or pembrolizumab within its marketing authorisation for untreated advanced 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 cases[1]. There are several types of RCC. The main ones are clear cell (around 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 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. Because of the nature of symptoms, kidney cancer is often diagnosed at an advanced stage. On average 44% of people diagnosed with kidney cancer have stage 3 or 4 disease[3]. 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 2017, 10,759 new kidney cancer cases were diagnosed in England, of which around 8,607 would be new cases of RCC[3]. 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 cancer[4].

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 645 recommends avelumab with axitinib for use within the Cancer Drugs Fund for untreated advanced renal cell carcinoma. 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. NICE technology appraisal 650 does not recommend pembrolizumab with axitinib for untreated advanced RCC.

The technology

Lenvatinib (Kisplyx, Eisai) is a multiple receptor tyrosine kinase inhibitor that selectively inhibits vascular endothelial growth factor (VEGF) receptors and other receptor tyrosine kinases that are involved in tumour proliferation. It is administered orally.

Everolimus (Afinitor, Novartis) is an oral active inhibitor of the mammalian target of rapamycin (mTOR) protein, a central regulator of tumour cell division and blood vessel growth in cancer cells. It is administered orally.

Pembrolizumab (Keytruda, Merck Sharp & Dohme) is a humanised, antiprogrammed cell death 1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. It is administered intravenously.

Lenvatinib has a marketing authorisation in the UK in combination with everolimus for the treatment of adult patients with advanced RCC following prior vascular endothelial growth factor (VEGF)-targeted therapy.

Lenvatinib with everolimus or pembrolizumab does not currently have a marketing authorisation in the UK for untreated advanced RCC. It has been studied in a randomised clinical trial, compared with sunitinib, in adults with untreated advanced RCC.

Intervention(s)	Lenvatinib with everolimus or Lenvatinib with pembrolizumab
Population(s)	People with untreated advanced renal cell carcinoma
Comparators	• Pazopanib • Sunitinib • Tivozanib • Cabozantinib (only for intermediate- or poor-risk disease as defined in the IMDC criteria) • Nivolumab with ipilimumab (only for intermediate- or poor-risk disease as defined in the IMDC criteria) – subject to ongoing CDF review

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 and subsequent treatment technologies will be taken into account. The availability of any managed access arrangement for the intervention 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:** Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma (2020) NICE technology appraisal guidance 650. Review date 2023. Avelumab with axitinib for untreated advanced renal cell carcinoma (2020) NICE technology appraisal guidance 645. Review date TBC. Nivolumab with ipilimumab for untreated advanced renal cell carcinoma (2019) NICE technology appraisal guidance 581. Review date 2021. Cabozantinib for untreated advanced renal cell carcinoma (2018) NICE technology appraisal guidance 542. Review date 2021. Tivozanib for treating renal cell carcinoma (2018) NICE technology appraisal guidance 512. Review date 2021.

	Pazopanib for the first-line treatment of advanced renal cell carcinoma (2011, updated 2013) NICE technology appraisal guidance 215. Static list. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (2009, updated 2017) NICE technology appraisal guidance 169. Static list. 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. Static list. **Appraisals in development:** Nivolumab with cabozantinib for untreated advanced or metastatic renal cell carcinoma [ID1625]. NICE technology appraisal guidance. Publication expected 16 June 2021. **Related guidelines:** Suspected cancer: recognition and referral (2015 updated 2017) NICE guideline NG12. Static list. Improving outcomes in urological cancers (2002) Cancer service guideline CSG2. Review date TBC. **Related NICE Pathways:** Renal cancer (2017) NICE pathway http://pathways.nice.org.uk/pathways/renal-cancer
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

In NHS clinical practice, when would you expect lenvatinib to be used with pembrolizumab and when with everolimus?

Would the dose of lenvatinib used in clinical practice differ depending on whether it was given with everolimus or pembrolizumab?

Have all relevant comparators for lenvatinib with everolimus or lenvatinib with pembrolizumab been included in the scope?

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

Are the outcomes listed appropriate?

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

Where do you consider lenvatinib with everolimus or lenvatinib with pembrolizumab will fit into the existing NICE pathway, renal cancer?

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 lenvatinib with everolimus or lenvatinib with pembrolizumab 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 lenvatinib with everolimus or lenvatinib with pembrolizumab 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 lenvatinib with everolimus or lenvatinib with pembrolizumab 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).

References

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

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