NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Health Technology Appraisal

Belzutifan for untreated renal cell carcinoma caused by von Hippel-Lindau disease

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of belzutifan within its marketing authorisation for untreated clear-cell renal cell carcinoma caused by von Hippel-Lindau disease.

Background

Von Hippel-Lindau disease (VHL) is an inherited disorder causing multiple tumours, both benign and malignant, in the central nervous system and organs. It is caused by a mutation (fault) in the VHL gene. Renal cell carcinoma (RCC) is one of the most common tumours resulting from VHL. 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 subtypes of RCC, including clear cell, papillary and chromophobe. All RCCs caused by VHL are of the clear cell subtype.

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 30% of those who have surgery develop advanced disease later on.[4-5]

VHL affects around 0.3 in 10,000 people in the European Union,[6] which equates to around 1,300 adults in England.[7] RCC occurs in around 24% to 45% of people with VHL.[8] 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.[9] People with stage 1 to 3 clear-cell RCC caused by VHL who have undergone have nephrectomy have improved survival compared with those without VHL.[10]

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 RCC who have not had 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 RCC. 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

Belzutifan (brand name unknown, Merck Sharp & Dohme) selectively targets a protein called hypoxia inducible factor (HIF) - 2α. HIF-2α levels are raised in people with VHL, which can lead to the growth of both benign and malignant tumours. By blocking the activity of HIF-2α, it is expected that belzutifan will slow down worsening of VHL and improve symptoms. Belzutifan is administered orally.

Belzutifan does not currently have a market authorisation in the UK for treating clear-cell RCC caused by VHL. It has been studied in a single-arm, open-label trial in adults with untreated VHL-associated clear-cell RCC.

Intervention(s)	Belzutifan
Population(s)	Adults with untreated clear-cell renal cell carcinoma caused by von Hippel-Lindau disease
Comparators	• Sunitinib • Pazopanib • 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 • Avelumab with axitinib – subject to ongoing CDF review • Lenvatinib with everolimus or pembrolizumab – subject to ongoing NICE appraisal
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 advanced 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 'Nivolumab with ipilimumab for untreated advanced renal cell carcinoma' (2019) NICE technology appraisal guidance 581. Review date August 2021 'Cabozantinib for untreated advanced renal cell carcinoma' (2018) NICE technology appraisal guidance 542. Review date 2021 'Tivozanib for treating advanced 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 '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) NICE technology appraisal guidance 178. Static list

	'Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' (2009) NICE technology appraisal guidance 169. Static list Appraisals in development (including suspended appraisals) 'Lenvatinib with everolimus or pembrolizumab for untreated advanced renal cell carcinoma' NICE technology appraisals guidance [ID3760] Publication expected January 2023 'Nivolumab with cabozantinib for untreated advanced or metastatic renal cell carcinoma' NICE technology appraisals guidance [ID1625] Suspended April 2021 'Atezolizumab plus bevacizumab for untreated locally advanced or metastatic renal cell carcinoma' NICE technology appraisals guidance [ID1365] Suspended November 2018 'Renal cell carcinoma - sunitinib' NICE technology appraisals guidance [ID1076] Suspended December 2018 'Savolitinib for treating MET-driven unresectable advanced papillary renal cell carcinoma' NICE technology appraisal guidance [ID1638] Suspended April 2020 Related Guidelines: Suspected cancer: recognition and referral (2015 updated 2017) NICE guideline NG12 Improving outcomes in urological cancers (2002) Cancer service guideline CSG2 Related Interventional Procedures: Irreversible electroporation for treating renal cancer (2013) NICE Interventional Procedures Guidance 443 Laparoscopic cryotherapy for renal cancer (2011) NICE Interventional Procedures Guidance 405 Percutaneous cryotherapy for renal cancer (2011) NICE Interventional Procedures Guidance 402 Percutaneous radiofrequency ablation for renal cancer (2010) NICE Interventional Procedures Guidance 353 Related NICE Pathways: Renal cancer (2021) NICE Pathway
Related National Policy	The NHS Long Term Plan, 2019. NHS Long Term Plan NHS England (2018) NHS England Funding and Resource 2018/19: Supporting 'Next Steps for the NHS Five Year Forward View' NHS England (2018) Manual for Prescribed Specialised Services 2018/19 Chapter 9 Adult Specialist Endocrinology Service NHS England commissions services for von Hippel Lindau disease (section G)

	NHS England (2018/2019) NHS manual for prescribed specialist services (2018/2019) Department of Health (April 2016) NHS Outcomes Framework 2016-2017: Domains 1 and 2. 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 Department of Health (2011) Improving outcomes: a strategy for cancer Department of Health (2009) Cancer commissioning guidance

Questions for consultation

Which treatments are considered to be established clinical practice in the NHS for clear-cell RCC caused by von Hippel-Lindau disease? Is RCC caused by von Hippel-Lindau disease treated differently to RCC from other causes?

Have all relevant comparators for belzutifan for treating clear-cell RCC caused by von Hippel-Lindau disease been included in the scope?

Are the outcomes listed appropriate?

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

Where do you consider belzutifan 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 belzutifan 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 belzutifan 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 belzutifan 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 April 2021.

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. Leibovich, B.C., Blute, M.L., Cheville, J.C., Lohse, C.M., Frank, I., Kwon, E.D., Weaver, A.L., Parker, A.S. and Zincke, H. (2003), Prediction of progression after radical nephrectomy for patients with clear cell renal cell carcinoma. Cancer, 97:1663-1671. Available from: https://doi.org/10.1002/cncr.11234

5. Ljungberg, Alamdari, Rasmuson, and Roos, (1999), Follow-up guidelines for nonmetastatic renal cell carcinoma based on the occurrence of metastases after radical nephrectomy. BJU International, 84: 405-411. Available from: https://doi.org/10.1046/j.1464-410x.1999.00202.x

6. European Medicines Agency (2020). EU/3/20/2324. Accessed May 2021

7. Office for National Statistics (2020). Population estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019. Accessed May 2021

8. Cancer Therapy Advisor (2018). VHL and the Risk for Renal Cell Carcinoma — In the Clinic. Accessed May 2021

9. Cancer Research UK (2019). Kidney cancer survival statistics. Accessed April 2021.

10. Yao M. et al. (2002) VHL tumor suppressor gene alterations associated with good prognosis in sporadic clear-cell renal carcinoma. J Natl Cancer Inst. 94(20):1569-75