NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Multiple Technology Appraisal

Axitinib, everolimus, nivolumab, sorafenib and sunitinib for previously treated advanced or metastatic renal cell carcinoma (incl. review of TA333 and TA219, and part review of TA178)

Draft scope

Draft remit/appraisal objective

To appraise the clinical and cost effectiveness of axitinib, everolimus, nivolumab, sorafenib and sunitinib, within their marketing authorisations, for treating advanced or metastatic renal cell carcinoma that has been previously treated.

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 (approximately 90% of the cases).[0] There are several different types of RCC, with the main ones divided into five categories: clear cell, papillary (Types 1 and 2), chromophobe, oncocytic and collecting duct carcinoma. Clear cell is the most common form of RCC accounting for approximately 80-90% of cases.[0]

The tumour node metastases system is used to grade RCC into stages I to IV. Advanced RCC, in which the tumour is either locally advanced and/or has spread to regional lymph nodes, is generally defined as stage III. Metastatic RCC, in which the tumour has spread beyond the regional lymph nodes to other parts of the body, is generally defined as stage IV.

Early, small RCC tumours are usually asymptomatic; the diagnosis of early RCC is usually incidental after abdominal scans for other indications. The most common presenting symptoms of metastatic and/or 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. Nephron sparing surgery may be curative in people with localised tumours. However, around half of those who have curative resection for earlier stages of the disease develop advanced and/or metastatic disease later on.

In 2011, 8369 new kidney cancer cases were diagnosed in England.[0] In 2006, approximately 26% of people diagnosed with RCC had stage III disease and 17% had stage IV disease.[0] The 5-year survival rate for metastatic RCC is approximately 10%.[0]

The aim of treatment is to stop the growth of new blood vessels within the tumour. NICE recommends sunitinib for previously untreated people with advanced and/or metastatic RCC for whom immunotherapy is suitable and who have an Eastern Cooperative Oncology Group (ECOG) status of 0 or 1 (NICE technology appraisal guidance 169). Pazopanib is also recommended for people who have not received prior cytokine therapy and have an ECOG status of 0 or 1 (NICE technology appraisal guidance 215). Current NICE guidance does not recommend bevacizumab, sorafenib or temsirolimus for previously untreated advanced or metastatic RCC (technology appraisal guidance 178). After failure of prior systemic treatment with a tyrosine kinase inhibitor or cytokine, NICE technology appraisal guidance 333 recommends axitinib. Because the remit referred to NICE by the Department of Health for axitinib only includes adults who have been previously treated with sunitinib, the use of axitinib after treatment with other tyrosine kinase inhibitors is not subject to statutory funding. This recommendation will be reviewed within this MTA. Everolimus, sorafenib and sunitinib are not recommended after initial therapies had failed in NICE guidance (NICE technology appraisal guidance 178 and 219); however, everolimus is available in England for metastatic RCC via the Cancer Drugs Fund for some patients. The recommendations in technology appraisal guidance 219, and those in technology appraisal 178 on sorafenib and sunitinib for previously treated advanced or metastatic RCC, will be reviewed within this MTA.

The technology

Axitinib (Inlyta, Pfizer) is an inhibitor of vascular endothelial growth factor receptor tyrosine kinases. It has a marketing authorisation in the UK for the treatment of adults with advanced renal cell carcinoma after failure of previous treatment with sunitinib or a cytokine.

Everolimus (Afinitor, Novartis) is a protein kinase inhibitor. It has a marketing authorisation in the UK for the treatment of people with advanced renal cell carcinoma, whose disease has progressed on or after treatment with VEGF-targeted therapy.

Sorafenib (Nexavar, Bayer) is an inhibitor of multiple intracellular and cell surface kinases thought to be involved in angiogenesis (the growth of new blood vessels). It has a marketing authorisation in the UK for the treatment of people with advanced renal cell carcinoma whose disease has failed previous interferon-alpha or interleukin-2 based therapy, or who are considered unsuitable for such therapy.

Sunitinib (Sutent, Pfizer) is an inhibitor of several receptor tyrosine kinases. It has a marketing authorisation in the UK for the treatment of advanced/metastatic renal cell carcinoma in adults.

Nivolumab (Opdivo, Bristol-Myers Squibb) is a human immunoglobulin G4 monoclonal antibody that binds to the cell surface receptor programmed

death-1(PD-1; a negative immuno-regulatory protein), thereby activating an immune response to tumour cells. Nivolumab does not currently have a marketing authorisation in the UK for treating renal cell carcinoma. It has been studied in clinical trials, compared with everolimus, in adults with advanced or metastatic clear-cell RCC who have received previous anti-angiogenic therapies.

All the technologies except nivolumab are given orally. Nivolumab is given intravenously.

Intervention(s)	For people who have received previous cytokine therapy (aldesleukin or interferon alfa): • Axitinib • Sorafenib • Sunitinib For people who have received previous VEGF-targeted therapy: • Axitinib • Everolimus • Nivolumab • Sunitinib
Population(s)	People with previously treated, advanced or metastatic renal cell carcinoma.
Comparators	For people who have received previous cytokine therapy (aldesleukin or interferon alfa): • The interventions listed above compared with each other • Pazopanib • Best supportive care For people who have received previous VEGF-targeted therapy: • The interventions listed above compared with each other • Best supportive care

Outcomes	The outcome measures to be considered include: • overall survival • progression-free survival • response rate • 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 patient access schemes for the intervention or comparator technologies will be taken into account.
Other considerations	If the evidence allows the following subgroups will be considered. These include: • previous treatment • prognostic score (for example, ECOG or Motzer). Guidance will only be issued in accordance with the marketing authorisation.
Related NICE recommendations and NICE Pathways	**Related Technology Appraisals**: 'Axitinib for treating advanced renal cell carcinoma after failure of prior systemic treatment' (2015). NICE Technology Appraisal 333. Reviewed within this MTA. 'Everolimus for the second-line treatment of advanced renal cell carcinoma' (2011). NICE Technology appraisal 219. Reviewed within this MTA. 'Pazopanib for the first-line treatment of advanced renal cell carcinoma' (2011). NICE Technology appraisal 215. Guidance on the 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 178. Part reviewed within this MTA. 'Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma' (2009). NICE Technology appraisal 169. Guidance on static list. *Appraisals in development (including suspended appraisals)* 'Pazopanib for the second line treatment of metastatic renal cell carcinoma (discontinued)' NICE technology appraisals guidance [ID70]. **Related Guidelines**: 'Referral guidelines for suspected cancer' (2005). NICE guideline 27 Review date June 2015. 'Improving outcomes in urological cancers' (2002). NICE guideline CSGUC. Review date to be confirmed. **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 (2015) NICE pathway
Related National Policy	NHS England (January 2014) Manual for prescribed specialised services. Section 105 (p236) http://www.england.nhs.uk/wp-content/uploads/2014/01/pss-manual.pdf NHS England: B14. Specialised Urology. NHS Care and Clinical Reference Groups. Link accessed: 26th February 2015 http://www.england.nhs.uk/commissioning/spec-services/npc-crg/group-b/b14/ Department of Health, NHS Outcomes Framework 2014-2015, Nov 2013. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/256456/NHS_outcomes.pdf

	Department of Health (2014) The national cancer strategy: 4th annual report https://www.gov.uk/government/publications/the-national-cancer-strategy-4th-annual-report Department of Health (2011) Improving outcomes: a strategy for cancer https://www.gov.uk/government/publications/the-national-cancer-strategy Department of Health (2009) Cancer commissioning guidance http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_110115 Department of Health (2007) Cancer reform strategy http://webarchive.nationalarchives.gov.uk/20130107105354/http:/www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_081006

Questions for consultation

Have all relevant comparators for axitinib, everolimus, nivolumab, sorafenib and sunitinib been included in the scope? Which treatments are considered to be established clinical practice in the NHS for advanced or metastatic renal cell carcinoma?

Is pazopanib routinely used in clinical practice for people who have received previous cytokine therapy for advanced or metastatic renal cell carcinoma?

How should best supportive care be defined?

Are the outcomes listed appropriate?

Are the subgroups suggested in 'other considerations appropriate? Are there any other subgroups of people in whom axitinib, everolimus, nivolumab, sorafenib and sunitinib are expected to be more clinically effective and cost effective or other groups that should be examined separately?

Where do you consider axitinib, everolimus, nivolumab, sorafenib and sunitinib 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 axitinib, everolimus, nivolumab, sorafenib and sunitinib are/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 axitinib, everolimus, nivolumab, sorafenib and sunitinib to be innovative in their potential to make a significant and substantial impact on health-related benefits and how they 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 axitinib, everolimus, nivolumab, sorafenib and sunitinib 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.

NICE intends to appraise axitinib, everolimus, nivolumab, sorafenib and sunitinib through its Multiple Technology Appraisal (MTA) Process. Is it appropriate to appraise nivolumab 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 American Cancer Society (2014) Kidney Cancer (Adult) - Renal Cell Carcinoma. Accessed May 2015.
2 Patient.co.uk: Renal Cancer. Accessed May 2015.
3 Cancer Research UK (2011) Kidney cancer incidence statistics. Accessed May 2015.
4 GP Notebook: clear cell cancer. Accessed May 2015.