Innovation Observatory

NHS National Institute for Health Research

EVIDENCE BRIEFING SEPTEMBER 2018

Avelumab in combination with axitinib for advanced or metastatic renal cell carcinoma – first line

NIHRIO ID	12519	**NICE ID**	9156
Developer/Company	Merck Serono Ltd and Pfizer Ltd	**UKPS ID**	644770

Licensing and market availability plans	Currently in phase III clinical trials.

SUMMARY

Avelumab intravenous infusion in combination with oral axitinib is in clinical development for people with advanced or metastatic renal cell carcinoma that have not received any prior treatment. Renal cell carcinoma originates in the tubules of the kidney that filter the blood waste and is the most common type of kidney cancer in adults. Renal cell carcinoma is advanced when it has spread to regional lymph nodes and is metastatic when the tumour has spread to other parts of the body. Current treatment options are associated with severe adverse events, and in most patients disease will eventually progress.

Avelumab is a human monoclonal antibody that works by inducing cancer cell death and restoring immune response against cancer cells. Axitinib works by blocking the growth of blood vessels that supply the cancer cells. Their combined mechanism of actions may result in more effective cancer growth inhibition with manageable toxicity profiles. If licensed, avelumab in combination with axitinib may offer an additional treatment option for people with advanced renal cell carcinoma that have not been treated previously.

PROPOSED INDICATION

Previously untreated advanced (advanced or metastatic) renal cell carcinoma (RCC) – first line[a]

TECHNOLOGY

DESCRIPTION

Avelumab (Bavencio) is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against the human immunosuppressive ligand programmed death-ligand 1 (PD-L1) protein, with potential immune checkpoint inhibitory and antineoplastic activities. Upon administration, avelumab binds to PD-L1 and prevents the interaction of PD-L1 with its receptor programmed cell death protein 1 (PD-1) - a cell surface receptor belonging to the immunoglobulin superfamily expressed on T cells. This inhibits the activation of PD-1 and its downstream signalling pathways, which may restore immune function through the activation of cytotoxic T lymphocytes (CTLs) targeted to PD-L1-overexpressing tumour cells. In addition, avelumab induces an antibody-dependent cellular cytotoxic (ADCC) response against PD-L1-expressing tumour cells. PD-1 negatively regulates T-cell activation and effector function when activated by its ligand, and plays an important role in tumour evasion from host immunity. PD-L1, a transmembrane protein, is overexpressed on a variety of tumour cell types and is associated with poor prognosis.[1]

Axitinib (Inlyta) is an orally bioavailable tyrosine kinase inhibitor. Axitinib inhibits the proangiogenic cytokines vascular endothelial growth factor (VEGF) and platelet-derived growth factor receptor (PDGF), thereby exerting an anti-angiogenic effect.[2]

Avelumab in combination with axitinib is intended for the treatment of renal cell carcinoma in people that have not had previous treatment and their cancer is at an advanced stage of development. In the phase III clinical trial (JAVELIN Renal 101; NCT02684006), avelumab is administered intravenously (IV) at 10 mg/kg every two weeks in combination with axitinib orally given at 5 mg twice a day. Treatment duration is for 30 months.[3]

INNOVATION AND/OR ADVANTAGES

Although many patients with advanced renal-cell carcinoma who receive currently approved therapies show clinical benefit, the regimens are associated with severe adverse events, and in most patients disease will eventually progress. Therefore, novel therapies and regimens that can achieve clinical activity and survival improvements with manageable toxicity profiles are needed.

The combination of an immune checkpoint inhibitor (avelumab) and a VEGF pathway inhibitor (axitinib) to treat patients with advanced renal-cell carcinoma might increase the clinical benefit of these drugs compared with their use alone. Preliminary results from a phase 1b trial reported that the safety profile of the combination avelumab plus axitinib in treatment-naive patients with advanced renal-cell carcinoma seemed to be manageable and consistent with that of each drug alone, and the preliminary data on antitumour activity are encouraging.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Avelumab is licenced in the UK for the treatment of metastatic Merkel cell carcinoma.[5] The most common adverse reactions with avelumab were fatigue, nausea, diarrhoea, decreased appetite, constipation, infusion-related reactions, weight decreased and vomiting.[5]

[a] Information provided by Merck Serono Ltd on UK PharmaScan

Axitinib is licenced in the UK for the treatment of advanced renal cell carcinoma following failure of previous treatment with sunitinib or a cytokine (aldesleukin or interferon alfa).[6] The most common adverse reactions observed following treatment with axitinib were diarrhoea, hypertension, fatigue, decreased appetite, nausea, weight decreased, dysphonia, palmar-plantar erythrodysaesthesia (hand-foot) syndrome, haemorrhage, hypothyroidism, vomiting, proteinuria, cough, and constipation.[6]

Avelumab in combination with axitinib is currently at phase II of development for the following indications:[7]

- Non-small cell lung cancer or Urothelial cancer
- Localized clear cell renal cell carcinoma
- Glioblastoma (recurrent)

PATIENT GROUP

DISEASE BACKGROUND

Renal cell carcinoma (RCC) originates in the proximal renal tubular epithelium lining nephrons, which are a network of small tubules responsible for filtering waste products from blood. It occurs in a sporadic (nonhereditary) and a hereditary form, and both forms are associated with structural alterations of the short arm of chromosome 3 (3p).[8] There are several types of RCC. The main ones are clear cell (accounting for approximately 75% of cases), papillary and chromophobe.[9]

RCC is graded into stages I to IV. Stage III 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 IV.[9] At advanced stage macroscopic spread is present in 25% at presentation, typically to the lung or bone, but also the liver, adrenals, brain, and skin.[10]

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. 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.[9]

Living with RCC requires many daily adjustments including lifestyle changes such as stopping smoking (where relevant), keeping to a healthy weight, avoiding high protein diets (as these can stress the kidney), eating healthily, drinking plenty of water, avoiding products high in salts and avoiding some medications and supplements which may damage the kidney (e.g. painkillers like aspirin and ibuprofen). Living with RCC may also impact emotions and relationships, causing anxiety, fear and depression for the patient and relatives and friends.[11]

CLINICAL NEED AND BURDEN OF DISEASE

Renal cell cancer is the most common type of kidney cancer in adults. More than 8 in every 10 (80%) kidney cancers diagnosed in the UK are this type.[12] Kidney cancer is the 7th most common cancer in the UK, accounting for 3% of all new cancer cases. In England in 2016, there were a total of 4,608 newly diagnosed cases of kidney cancer (IDC-10 code C64).[13]

The incidence rate of kidney cancer cases in England in 2015 was 19.2 per 100,000. Incidence rates for kidney cancer are projected to rise by 26% in the UK from 21 cases per 100,000 in 2014 to 32 cases per 100,000 people by 2035.[14]

Five year survival estimates for 2011 to 2015 in RCC patients increased from 57.9% to 60.2% in men and from 60.1% to 62.0% in women. The proportion of men and women diagnosed with RCC at each stage was similar and the overall survival was nearly the same (77.7% for men and 78.8% for women in 2015). There was not much difference in survival between stages I to III, but much worse survival for those diagnosed at stage IV, which shows that people diagnosed at this stage died at more than twice the rate of the general population.[15]

In 2016/17, there were 19,056 finished consultant episodes (FCEs), 15,740 admissions and 56,957 FCE bed days due to malignant neoplasm of kidney (ICD-10 code: C64) in England and Wales.[16]

Between 25% and 31% of people have metastases at diagnosis.[17] Based on 2014 incidence of 11,102 cases in England and Wales, this would equate to between 2,775 and 3,442 persons with metastases per year who may be eligible for avelumab in combination with axitinib as first-line treatment. This is an underestimate of the potential treated population at diagnosis as the percentage of people with advanced RCC but no metastases could not be ascertained.

PATIENT TREATMENT PATHWAY

PATIENT PATHWAY

Patients with locally advanced RCC undergo open radical nephrectomy (RN), although partial nephrectomy may be considered.[18] Open RN remains the standard of care even though a laparoscopic approach can be considered. In those where metastasis have occurred, metastasectomy and other local treatment strategies including whole brain radiotherapy (WBRT), conventional radiotherapy, stereotactic radiosurgery (SRS), stereotactic body radiotherapy (SBRT), cyberknife radiotherapy and hypofractionated radiotherapy can be considered and carried out for selected patients after multidisciplinary review.

CURRENT TREATMENT OPTIONS

The aim of treatment is to prevent the growth and survival of cancer cells within the tumour.[9] NICE has provided recommendations for the first line treatment (people that have had no previous treatment) of advanced and metastatic renal cancer that include the following drug treatments:[19]

- Tivozaniv
- Pazopanib
- Sunitinib
- Cabozantinib[20]

Radiotherapy is an effective treatment for palliation of local and symptomatic metastatic RCC disease or to prevent the progression of metastatic disease in critical sites such as the bones or brain. For symptomatic bone metastases, local radiotherapy (either as a single fraction or as fractionated course) can provide good symptom relief in up to two-thirds of cases with complete symptomatic responses in up to 20% to 25%.[21]

PLACE OF TECHNOLOGY

If licensed, avelumab in combination with axitinib may offer an additional first line treatment option for patients with metastatic or advanced renal cell carcinoma who have not undergone prior systemic therapy. If licensed for this indication, avelumab in combination with axitinib would be the first tyrosine kinase inhibitor (TKI) and immunotherapy (IO) combination therapy available for this patients at first line.

CLINICAL TRIAL INFORMATION

Trial	**JAVELIN Renal 101, B9991003, NCT02684006, 2015-002429-20 (EudraCT Number); adults aged over 18; avelumab in combination with axitinib vs sunitinib; phase III**
Sponsor	Pfizer Ltd
Status	Ongoing
Source of Information	Trial registry[3]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, active-controlled, open-label
Participants	n=888; aged over 18 years; histologically or cytologically confirmed advanced or metastatic RCC with clear cell component; no prior systemic therapy directed at advanced or metastatic RCC.
Schedule	Randomised to either: • Avelumab administered at 10 mg/kg IV every two weeks in combination with axitinib, 5 mg orally twice a day • Sunitinib given at 50 mg orally once a day on schedule 4/2
Follow-up	Active treatment period not reported. Follow-up up to 5 years.
Primary Outcomes	• Progression Free Survival (PFS) in PD-L1 positive patients [Time Frame: From randomization up to 30 months.] • Overall Survival in PD-L1 positive patients [Time Frame: Every 3 months up to 5 years]
Secondary Outcomes	• Overall Survival (OS) in unselected patients [Time Frame: Every 3 months up to 5 years] • Number of participants with Objective Response (OR) [Time Frame: Every 6 weeks up to 18 months from patient enrolment in the study, then every 12 weeks up to 30 months from randomization] • Disease Control (DC) [Time Frame: Every 6 weeks up to 18 months from patient enrolment in the study, then every 12 weeks up to 30 months from randomization] • Time to Tumour Response (TTR) [Time Frame: Every 6 weeks up to 18 months from patient enrolment in the study, then every 12 weeks up to 30 months from randomization] • Duration of response (DR) [Time Frame: Every 6 weeks up to 18 months from patient enrolment in the study, then every 12 weeks up to 30 months from randomization]

	• Progression Free Survival (PFS) by Investigator assessment [Time Frame: Every 6 weeks up to 18 months from patient enrolment in the study, then every 12 weeks up to 30 months from randomization] • Trough plasma concentration (Ctrough) of avelumab [Time Frame: Pre-dose] • Ctrough is defined as the concentration at the end of avelumab dosage interval • Trough plasma concentration (Ctrough) of axitinib [Time Frame: Pre-dose] • Ctrough is defined as the concentration at the end of axitinib dosage interval • Maximum plasma concentration (Cmax) of axitinib [Time Frame: 2 hours post-dose] • Anti-Drug Antibody (ADA) levels of avelumab/Neutralizing antibodies titres for MSB0010718C [Time Frame: Pre-dose] • Immunogenicity assessment of avelumab • Tumour tissue biomarker status [Time Frame: Baseline] • Overall Survival (OS) in biomarker-positive and biomarker-negative subgroups [Time Frame: Baseline] • Change From Baseline in FACT-Kidney Symptom Index (FKSI)-19 [Time Frame: Every 6 weeks up to 3 years] • Change from Baseline in European Quality of Life Questionnaire (EQ-5D) - Health State Profile [Time Frame: Every 6 weeks up to 3 years] • EQ-5D Health State Profile: participant rated questionnaire to assess health-related quality of life in terms of a single index value. • Progression Free Survival (PFS) in biomarker-positive and biomarker-negative subgroups [Time Frame: Baseline] • Objective Response (OR) in biomarker-positive and biomarker-negative subgroups [Time Frame: Baseline] • Disease Control (DC) in biomarker-positive and biomarker-negative subgroups [Time Frame: Baseline] • Time To Response (TTR) in biomarker-positive and biomarker-negative subgroups [Time Frame: Baseline] • Duration of Response (DR) in biomarker-positive and biomarker-negative subgroups [Time Frame: Baseline] • Change from Baseline in European Quality of Life Questionnaire (EQ-5D) - Visual Analogic Scale [Time Frame: Every 6 weeks up to 3 years]

	• Time to treatment discontinuation/failure due to toxicity (TTF) [Time Frame: From Cycle 1 Day 1, every 6 weeks up to the End of Treatment] • Treatment discontinuation/failure due to toxicity [Time Frame: From Cycle 1 Day 1, every 6 weeks up to the End of Treatment] • PFS on next-line therapy (PFS2) [Time Frame: From randomization up to 5 years.] • Progression Free Survival (PFS) in unselected patients [Time Frame: From randomization up to 30 months.]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as December 2018, study completion date reported as Jan 2021

ESTIMATED COST

The cost of avelumab 20 mg per 1 ml for the current licensed indication is £768.00.[5]

The cost of axitinib for the current licensed indications is as follows:[6]

- Axitinib 1 mg £703.40
- Axitinib 3 mg £2110.20
- Axitinib 5 mg £3517.00
- Axitinib 7 mg £4923.80

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma (ID1426, GID-TA10331). Expected publication to be confirmed.
- NICE technology appraisal in development. Atezolizumab plus bevacizumab for untreated locally advanced or metastatic renal cell carcinoma (ID1365, GID-TA10338). Expected publication date to be confirmed.
- NICE technology appraisal in development. Cabozantinib for untreated locally advanced or metastatic renal cell carcinoma (ID1208, GID-TA10231). Expected publication date October 2018
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma (ID1182, GID-TA10189). Expected publication date October 2018
- NICE technology appraisal. Tivozanib for treating advanced renal cell carcinoma (TA512). March 2018

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- NICE technology appraisal. 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 (TA178). August 2009
- NICE technology appraisal. Sunitinib for the first-line treatment of advanced and/or metastatic renal cell carcinoma (TA169). March 2009

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. National cancer drugs fund list. August 2018
- NHS England. 2013/14 NHS Standard Contract for cancer: Specialised kidney, bladder and prostate cancer services (Adult). B14/S/a
- Department of Health. The NHS outcomes framework 2014/15. November 2015

OTHER GUIDANCE

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NB: This briefing presents independent research funded by the National Institute for Health Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.