National Institute for Health Research

NIHR Innovation Observatory
Evidence Briefing: January 2018

Pembrolizumab in combination with axitinib for metastatic renal cell carcinoma – first line

NIHRIO (HSRIC) ID: 13640 NICE ID: 9416

LAY SUMMARY

Renal cell carcinoma (RCC) is the most common type of kidney cancer. Many people with RCC show no symptoms for many years and are often diagnosed late, after the cancer has spread (metastasised). RCC affects the lining of nephrons, which are a network of small tubules responsible for filtering waste products from blood. Symptoms include blood in urine, feeling of lump or mass in the kidney area, weight loss, raised temperature and sweating, back pain on one side (below the ribs), tiredness, loss of appetite and a general feeling of poor health.

Pembrolizumab (Keytruda®) is a type of immunotherapy that stimulates the body's immune system to fight cancer cells. Pembrolizumab targets and blocks a protein called PD-L1 on the surface of certain immune cells called T-cells. Blocking the PD-L1 protein allows the T-cells to find and kill the cancer cells. Axitinib (Inlyta®) is already marketed for the treatment of advanced and/or metastatic RCC. Axitinib reduces the growth and spread of cancer cells by inhibiting the growth of the blood vessels that supply blood to the cancer cells. If licensed, pembrolizumab in combination with axitinib will offer an additional treatment option for patients with metastatic RCC.

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.

TARGET GROUP

Renal cell carcinoma (RCC), metastatic – first line; in combination with axitinib

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda®), is a monoclonal antibody, a type of protein that has been designed to recognise and block a receptor called programmed death-1 (PD-1) receptor. Some cancers can make a protein that combines with PD-1 to switch off the activity of certain cells of the immune system preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer from switching off these immune cells, thereby increasing the ability of the immune system to kill the cancer cells.[1]

Axitinib works by blocking enzymes known as tyrosine kinases that are found in vascular endothelial growth factor (VEGF) receptors on the surface of cancer cells. VEGF receptors are involved in the growth and spread of cancer cells and in the development of blood vessels that supply the tumours. By blocking these receptors, axitinib helps to reduce the growth and spread of the cancer and cut off the blood supply that keeps the cancer cells growing.[2]

In the phase III trial, NCT02853331, participants receive pembrolizumab 200 mg intravenously every 3 weeks in combination with axitinib 5 mg orally twice daily over a course of 24 months.[3]

Pembrolizumab monotherapy is licensed in the UK for the following indications in adult patients:[4]

- Melanoma
- Non-small cell lung cancer (NSCLC) - locally advanced following prior chemotherapy, metastatic as first-line treatment or following prior chemotherapy
- Classical Hodgkin lymphoma
- Urothelial cancer

Pembrolizumab is most commonly associated with immune-related adverse reactions. Most of these, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of pembrolizumab.[5]

Axitinib is licensed in the UK for adult patients with advanced renal cell carcinoma after failure of prior treatment with sunitinib or a cytokine.[6,7] 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.[8]

Pembrolizumab is in phase III trials in Europe/USA for the following indications:[9]

- Breast Cancer
- Melanoma
- Non-small cell lung cancers
- Transitional cell cancers
- Head and Neck cancers

- Gastrointestinal cancers
- Multiple myeloma
- Hodgkin lymphoma
- Renal cell carcinoma (post nephrectomy)

Axitinib is in phase III trials for the following indications:[10]

- Pancreatic cancer
- Renal cancer
- Neuroendocrine tumours

INNOVATION and/or ADVANTAGES

If licensed, pembrolizumab in combination with axitinib will offer an additional treatment option for patients with metastatic renal cell cancer.

DEVELOPER

Merck Sharp & Dohme Ltd.

AVAILABILITY, LAUNCH or MARKETING

Pembrolizumab has no regulatory designation in the EU or US for renal cell carcinoma.

PATIENT GROUP

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).[11]

Specific RCC symptoms include blood in urine and feeling of lump or mass in the kidney area. Other vague symptoms include weight loss, a high temperature and very heavy sweating, a pain in the back on one side (below the ribs) that won't go away, tiredness, loss of appetite and a general feeling of poor health.[12]

Systemic metastases are common; macroscopic spread is present in 25% at presentation, typically to the lung or bone, but also the liver, adrenals, brain, and skin.[13]

Several factors increase a person's risk of developing RCC, including age, genetics, and exposure to risk factors (including some potentially avoidable lifestyle factors). An estimated 42% of RCCs in the UK are linked to lifestyle factors including smoking (24%) and overweight and obesity (24%). Ionising radiation, certain occupational exposures, and certain medicines also cause RCC. Certain medical conditions and inadequate physical activity may relate to higher RCC risk.[14]

CLINICAL NEED and BURDEN OF DISEASE

RCC was the seventh most common cancer in the UK in 2014 according to Cancer Research UK. The incidence of RCC was 11,102 new cases in England and Wales, and the UK incidence rate was 21.1 per 100,000 population.[15] Over the last decade, RCC incidence rates have increased by around two-fifths (41%), and are projected to rise to 32 cases per 100,000 in the UK by 2035.[14]

According to the Office of National Statistics, 5-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.[16] 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 1 to 3, but much worse survival for those diagnosed at stage 4, which shows that people diagnosed at this stage died at more than twice the rate of the general population.[16]

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.[17]

Between 25% and 31% of people have metastases at diagnosis.[14] Based on 2014 incidence of 11,102 cases in England and Wales, this would equate to between 2,775 and 3,442 persons per year who may be eligible for pembrolizumab with axitinib as first-line treatment.

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Cabozantinib for untreated locally advanced or metastatic renal cell carcinoma (ID1208). Expected publication date: October 2018.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [ID1182]. Expected publication date: October 2018.
- NICE technology appraisal. Pazopanib for the first-line treatment of advanced renal cell carcinoma (TA215). August 2013.
- 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.
- NICE interventional procedure guidance. Irreversible electroporation for treating renal cancer (IPG443). February 2013.
- NICE interventional procedure guidance. Laparoscopic cryotherapy for renal cancer (IPG405). August 2011.
- NICE interventional procedure guidance. Percutaneous cryotherapy for renal cancer (IPG402). July 2011.
- NICE interventional procedure guidance. Laparoscopic partial nephrectomy (IPG151). January 2006.
- NICE interventional procedure guidance. Laparoscopic nephrectomy (including nephroureterectomy) (IPG136). August 2005
- NICE interventional procedure guidance. Percutaneous radiofrequency ablation for renal cancer (IPG353). July 2010.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Children, Teenagers and Young Adults). B12/S/b.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- Renal Cell Carcinoma: ESMO Clinical Practice Guidelines. 2016.[18]
- EAU Guidelines on Renal Cell Carcinoma. European Association of Urology 2016.[19]
- NCCN Clinical Practice Guidelines in Oncology. Kidney Cancer. Version 2. 2017.[20]
- London Cancer. Guidelines for Renal Cancer. Version 1.0. Review 2015.[21]
- Clinical Practice Guidelines for the Treatment of Metastatic Renal Cell Carcinoma: Today and Tomorrow. 2011.[22]

CURRENT TREATMENT OPTIONS

According to NICE guidelines, first-line treatment for metastatic RCC include the following:[23,24]

- Pazopanib
- Sunitinib

The European Association of Urology (EAU) guidelines on RCC recommend:[19]

- Local therapy of advanced/metastatic RCC
    - Cytoreductive nephrectomy
    - Embolisation of the primary tumour
- Local therapy of metastases in mRCC
    - Complete versus no/incomplete metastasectomy
    - Local therapies for RCC bone metastases
    - Local therapies for RCC brain metastases
    - Embolisation of metastases
- Systemic therapy for advanced/metastatic RCC
    - Chemotherapy
    - Immunotherapy
      IFN-α monotherapy and combined with bevacizumab
      Interleukin-2
      Vaccines and targeted immunotherapy
      Immune checkpoint blockade
- Targeted therapies
    - sorafenib (Nexavar®)
    - sunitinib (Sutent®)
    - bevacizumab (Avastin®) combined with IFN-α
    - pazopanib (Votrient®)
    - temsirolimus (Torisel®)

- everolimus (Afinitor®)
- axitinib (Inlyta®)

In the era of immunotherapy, cytoreductive nephrectomy was recommended in patients with good performance status (PS) (one of the risk factors used in the Memorial Sloane Kettering Cancer Centre (MSKCC) or Motzer score to predict survival in metastatic RCC patients). In routine practice, cytoreductive nephrectomy is recommended in patients with good PS and large primary tumours with limited volumes of metastatic disease, and for patients with a symptomatic primary lesion. Cytoreductive nephrectomy is not recommended in patients with poor PS.[18]

EFFICACY and SAFETY

Trial	KEYNOTE-426, MK-3475-426, NCT02853331; pembrolizumab in combination with axitinib vs sunitinib monotherapy; phase III
Sponsor	Merck Sharp & Dohme Corp.
Status	Ongoing
Source of Information	Trial Registry[3]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, open label
Participants	n=840 (planned); aged 18 years and older; renal cell cancer; clear cell, metastatic; first line
Schedule	Randomised to pembrolizumab 200 mg intravenously every 3 wks plus axitinib 5 mg orally twice daily, or to sunitinib 50 mg orally once daily for 4 wks and then off treatment for 2 wks
Follow-up	Active treatment for 24 mths, follow-up to 39 mths
Primary Outcomes	• Progression-Free Survival (PFS) • Overall Survival (OS)
Secondary Outcomes	• Objective Response Rate (ORR) • Disease Control Rate (DCR) • Number of participants who experience an Adverse Event (AE) • Number of participants who discontinue study drug due to an AE • Duration of Response (DOR)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as Jan 2020

ESTIMATED COST and IMPACT

COST

Pembrolizumab is already marketed in the UK; a 50mg powder for solution for infusion vial costs £1,315 and treatment with 200mg every 3 weeks over a course of 24 months would cost £168,320.

Axitinib is already marketed in the UK; a pack of 56 x 5mg tablets costs £3,517 (£62.80 per tablet), and treatment with 5mg twice daily over a course of 24 months would cost approximately £91,693.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☒ Reduced mortality/increased length of survival

☐ Reduced symptoms or disability

☐ Other:

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☒ Increased use of existing services

☐ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other:

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs:

☐ Other reduction in costs:

☐ Other:

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified:

☒ None identified

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