

HEALTH TECHNOLOGY BRIEFING MAY 2020

Pembrolizumab for renal cell carcinoma - adjuvant therapy post nephrectomy

NIHRIO ID	20464	NICE ID	10205
Developer/Company	Merck Sharp & Dohme Ltd	UKPS ID	651362

Licensing and market availability plans

Currently in phase III clinical development.

*COMMERCIAL IN CONFIDENCE

SUMMARY

Pembrolizumab is in clinical development for the adjuvant treatment of advanced renal cell carcinoma (RCC), post nephrectomy (the surgical removal of a kidney). RCC is the most common form of cancer that originates in the kidney. It may occur due to the mutation of cells in the kidney's filtering system. RCC often has few symptoms, so may be diagnosed in advanced stages, when the cancer has spread to other organs.

Pembrolizumab is administered by intravenous infusion and works by improving the activity of white blood cells (T-cells) thereby increasing the ability of the immune system to kill cancer cells. Given as an adjuvant therapy, it is hoped pembrolizumab will help clear the remaining cancer cells after surgery to remove the cancerous kidney. If licenced, pembrolizumab will offer the first adjuvant therapy for patients with renal cell carcinoma post nephrectomy.

PROPOSED INDICATION

Adjuvant treatment of renal cell carcinoma (RCC) post nephrectomy.¹

TECHNOLOGY

DESCRIPTION

Pembrolizumab (Keytruda, MK-3475) is a humanised monoclonal antibody, which acts as PD-1 blockade agent. Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T cell proliferation and cytokine production. Upregulation of PD-1 ligands occur in some tumours and signalling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors.² Adjuvant therapy is a treatment that is given in addition to the primary (initial) treatment. In this case pembrolizumab is given after a nephrectomy, which is surgery to remove the kidney.³

Pembrolizumab is currently in clinical development for adjuvant therapy in patients with RCC. In the phase III clinical trial (NCT03142334) patients received pembrolizumab 200 mg via intravenous infusion on day 1 of each 3-week cycle for up to 17 cycles.¹

INNOVATION AND/OR ADVANTAGES

High-risk RCC is associated with a $\geq 40\%$ risk of recurrence after surgery. Adjuvant treatment for RCC has been an area of interest for clinicians to improve disease-free survival and overall survival (OS) in patients at high risk of recurrence. Systemic therapies, including cytokines and vascular endothelial growth factor (VEGF), tyrosine kinase inhibitors (TKIs) with efficacy in metastatic RCC (mRCC), have been evaluated in the adjuvant setting of RCC. However, none of these therapies demonstrated an improvement in OS among patients with high-risk RCC who had undergone nephrectomy.⁴

If licenced, pembrolizumab could provide an adjuvant therapy to address this unmet medical need in high-risk RCC patients, post-nephrectomy.

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Pembrolizumab is currently licenced as a monotherapy in the UK for the treatment of:⁵

- advanced (unresectable or metastatic) melanoma in adults
- as an adjuvant treatment of adults with stage III melanoma and lymph node involvement who have undergone complete resection
- metastatic non-small cell lung carcinoma (NSCLC) in adults whose tumours express PD-L1 with a $\geq 50\%$ tumour proportion score with no EGFR or ALK positive tumour mutations – first line
- locally advanced or metastatic NSCLC in adults whose tumour express PD-L1 with a $\geq 1\%$ TPS and who have received at least one prior chemotherapy regimen
- adult patients with relapsed or refractory classical Hodgkin lymphoma who have failed autologous stem cell transplant and brentuximab vedotin, or who are transplant ineligible and have failed BV
- locally advanced or metastatic urothelial carcinoma in adults who have received prior platinum-containing chemotherapy
- locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin containing chemotherapy and whose tumours express PD-L1 with a combined positive score ≥ 10

- recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) in adults whose tumours express PD-L1 with a $\geq 50\%$ TPS and progressing on or after platinum-containing chemotherapy
- as monotherapy or in combination with platinum and 5-fluorouracil chemotherapy, is indicated for the first-line treatment of metastatic or unresectable recurrent HNSCC in adults whose tumours express PD-L1 with a CPS ≥ 1 .

Pembrolizumab is also licensed in the UK in combination with:⁵

- pemetrexed and platinum chemotherapy for the first-line treatment of metastatic nonsquamous NSCLC in adults whose tumours have no EGFR or ALK positive mutations.
- carboplatin and either paclitaxel or nab-paclitaxel for the first-line treatment of metastatic squamous NSCLC in adults.
- axitinib is indicated for the first-line treatment of advanced RCC in adults.

Very common adverse events of pembrolizumab as monotherapy (affecting more than one in ten people) include anaemia, hypothyroidism, headache, decreased appetite, dyspnoea, cough, diarrhoea, abdominal pain, nausea, vomiting, constipation, rash, pruritus, musculoskeletal pain, arthralgia, fatigue, asthenia, oedema and pyrexia.⁵

Pembrolizumab is currently in phase III clinical trials for the treatment of multiple malignant conditions such as breast, cervical, endometrial, liver cancer and gastric cancer among others. It is also in phase II trials for advanced solid tumours.⁶

PATIENT GROUP

DISEASE BACKGROUND

RCC is the most common type of kidney cancer in adults. RCC starts in the lining of the tubules (the smallest tubes of the nephrons of the kidneys) which filter blood and make urine. There are several types of RCC depending on the type of cell in which the cancer originates, including: clear cell RCC (75% of RCCs), papillary (10% of RCCs) and chromophobe (5% of RCCs). The remaining types of RCC comprise of rare carcinomas of the collecting ducts and renal medullary carcinoma.⁷ RCC is high or intermediate-high risk when it is likely to either recur or spread.⁸

Several factors increase a person's risk of developing RCC including age, genetics, family history, and exposure to other risk factors. Risk factors include medical conditions such as thyroid cancer, inherited conditions such as Von Hippel-Lindau syndrome, dialysis treatment, high blood pressure, smoking, diabetes, and obesity.⁹

Patients with RCC can present with a range of symptoms including blood in the urine, a lump or mass in the kidney area, high temperature and very heavy sweating, persistent pain in the side of the back and loss of appetite. Unfortunately, many patients are asymptomatic until the disease is advanced.¹⁰ At diagnosis, approximately 25% of individuals either have distant metastases or advanced loco regional disease.¹¹ Paraneoplastic manifestations of RCC, including hypercalcaemia, production of adrenocorticotrophic hormone, polycythaemia, hepatic dysfunction, amyloidosis, fever, and weight loss are present in up to 20% of patients.¹² Living with RCC may also impact emotions and relationships, causing anxiety, fear and depression for the patient and relatives and friends.¹³

CLINICAL NEED AND BURDEN OF DISEASE

Kidney cancer is the 7th most common cancer in the UK, accounting for 4% of all new cancer cases. In females in the UK, kidney cancer is the 10th most common cancer, with around 4,900 new cases in 2017. In males, kidney cancer is the 6th most common cancer, with around 8,100 new cases in 2017. Incidence rates for kidney cancer are projected to rise by 26% in the UK between 2014 and 2035, to 32 cases per 100,000 people by 2035.¹⁴ Hospital admissions data for England in 2018-19 recorded 20,866 finished consultant episodes (FCE) for malignant neoplasm of kidney, except renal pelvis (ICD 10: C64), 17,674 hospital admissions and 8,510 day cases.¹⁵

Cancer-specific survival rates for non-metastatic clear cell RCC are estimated at 84% and 76% at 5 and 10 years respectively after initial surgical resection. However, around 30–40% of patients with high-risk features such as high nuclear grade, locally advanced stage, and/or regional lymph node involvement experience disease recurrence which is generally incurable.¹⁶

In 2017, kidney cancer was the 13th most common cause of cancer death in the UK accounting for 3% of all cancer deaths. Data from 2015-2017 estimates approximately 4,500 kidney cancer deaths in the UK each year.¹⁷ In 2018 there were 3,554 deaths in England and Wales with malignant neoplasm of kidney, except renal pelvis (ICD 10: C64) as the underlying cause of death.¹⁸

Kidney cancer is rare in young adults and children, but rates begin to rise after the age of 40 years. About three quarters of people diagnosed with kidney cancer (75%) are over 60 years old and the highest rates are in the 70-74 years age range for men and 75-79 years age range for women. More than a third of cases (36%) were diagnosed in people aged over 75 years between 2013 and 2015.¹⁹

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The treatment for kidney cancer depends on the size of the cancer and whether it has spread to other parts of the body.²⁰ Treatment decisions will be assessed by a multidisciplinary team including doctors, a specialist cancer nurse, symptom control specialists, dieticians, physiotherapists, psychologists and counsellors.²¹

Stage 1 and 2 kidney cancers contained in the kidney are often cured with surgery. Stage 3 cancers are called locally advanced cancers. They can sometimes be cured if the surgeon can remove all the cancer.²¹ Metastasectomy and other local treatment strategies including conventional radiotherapy, stereotactic radiosurgery, stereotactic body radiotherapy, CyberKnife® radiotherapy and hypofractionated radiotherapy can be considered and carried out for selected patients after multidisciplinary review.²² Other possible treatments include cryotherapy and arterial embolization.²¹

CURRENT TREATMENT OPTIONS

There are several different types of biological therapy used for the treatment of advanced kidney cancer, including immunotherapy, targeted therapies, and monoclonal antibodies.²³ However, currently there is no NICE recommended adjuvant therapy after nephrectomy for RCC.²⁴

PLACE OF TECHNOLOGY

If licenced, pembrolizumab will provide an adjuvant therapy for RCC in patients who have undergone nephrectomy.

CLINICAL TRIAL INFORMATION

Trial	MK-3475-564, KEYNOTE-564, NCT03142334 , EudraCT2016-004351-75 ; A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy in the Adjuvant Treatment of Renal Cell Carcinoma Post Nephrectomy Phase III Location(s): EU (incl UK), USA, Canada and other countries.
Trial design	Randomised, double-blind, placebo-controlled
Population	n=950 (planned); aged 18 years and older; RCC with clear cell component; intermediate-high risk, high risk, or M1 no evidence of disease (M1 NED); post nephrectomy, received no prior systemic therapy for advanced RCC.
Intervention(s)	Pembrolizumab 200mg via intravenous infusion on day 1 of each 3-week cycle for up to 17 cycles.
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome: <ul style="list-style-type: none">Disease-free survival (DFS) as assessed by the investigator [Time frame: up to approximately 72 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

ESTIMATED COST

Pembrolizumab is already marketed in the UK; a 100 mg/4 ml concentrate for solution for infusion vial (25mg/ml) costs £2,630.00, and 50 mg powder for concentrate for solution for infusion vial costs £1,315.00.²⁵

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE Interventional procedures guidance. Laparoscopic partial nephrectomy (IPG151). January 2006.

- NICE interventional procedures guidance. Laparoscopic nephrectomy (including nephroureterectomy) (IPG136). August 2005.
- NICE cancer service guideline. Improving outcomes in urological cancers (CSG2). September 2002.

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a.
- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

OTHER GUIDANCE

- European Society for Medical Oncology. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. 2019²²

ADDITIONAL INFORMATION

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