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Newcastle University

Health Technology Briefing
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Nivolumab with ipilimumab adjuvant therapy for renal cell carcinoma

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 14899	NICE ID: 9659	UKPS ID: 645158

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Nivolumab in combination with ipilimumab is in clinical development as adjuvant therapy for adult patients with localised renal cell carcinoma (RCC) who underwent partial or entire removal of a kidney. RCC (the most common type of kidney cancer in adults) is a disease that affects the lining of tiny tubes within the kidney which filter waste from the blood, making urine. Localised RCC means the cancer is either completely inside the kidney or has grown into surrounding tissues but has not spread to another part of the body. The main treatment for RCC is surgery to remove part or the whole kidney. After surgery, the disease may relapse and spread to other parts of the body. The aim of adjuvant treatment for localised RCC is to reduce the number of people whose disease relapses after surgery, and this remains an unmet need.

Nivolumab is a monoclonal antibody, a type of protein that has been designed to attach to a receptor called PD-1 found on cells of the immune system called T cells. By attaching to PD-1, nivolumab prevents cancer cells from switching off the activity of the T cells, thereby increasing the ability of the immune system to kill cancer cells. Ipilimumab is a monoclonal antibody designed to increase the number and the activity of T cells which can kill cancer cells. Ipilimumab acts on T cells by attaching to and blocking the activity of CTLA-4, a protein that controls the activity of T cells. Nivolumab and Ipilimumab are administered by intravenous infusion. If licensed, nivolumab with ipilimumab, administered intravenously, could provide an adjuvant treatment for localised renal cell carcinoma after surgery.

Proposed Indication

Adjuvant therapy for adult patients (aged 18 years and older) with localised RCC who underwent radical or partial nephrectomy and at high risk of relapse.[1]

Technology

Description

Nivolumab (Opdivo, BMS-936558) is a human immunoglobulin G4 (IgG4) monoclonal antibody (HuMAb), which binds to the programmed death-1 (PD-1) receptor and blocks its interaction with PD-L1 and PD-L2. Engagement of PD-1 with the ligands PD-L1 and PD-L2, which are expressed in antigen presenting cells and may be expressed by tumours or other cells in the tumour microenvironment, results in inhibition of T-cell proliferation and cytokine secretion. Nivolumab potentiates T-cell responses, including anti-tumour responses through blockade of PD-1 binding to PD-L1 and PD-L2.[2]

Ipilimumab (Yervoy, BMS-734016) is a cytotoxic T-lymphocyte antigen-4 (CTLA-4) immune checkpoint inhibitor that blocks T-cell inhibitory signals induced by the CTLA-4 pathway, increasing the number of reactive T-effector cells which mobilize to mount a direct T-cell immune attack against tumour cells. CTLA-4 blockade can also reduce T-regulatory cell function, which may contribute to an anti-tumour immune response. Ipilimumab may selectively deplete T-regulatory cells at the tumour site, leading to an increase in the intra-tumoural T-effector/ T-regulatory cell ratio which drives tumour cell death.[3]

Nivolumab in combination with ipilimumab is currently in clinical development as adjuvant therapy for adult patients with localised RCC who underwent partial or entire removal of a kidney and at high risk of relapse. In the phase III clinical trial (CheckMate 914, NCT03138512), patients received a specified dose of ipilimumab and nivolumab intravenously (IV) on specified days.[1]

Key Innovation

Surgery is standard treatment for nonmetastatic RCC. Unfortunately, patients with stage II or III RCC have high risk of relapse with 5-year disease-free survival rates of approximately 51%–56%; prevention of recurrence is an unmet need. In a previous study (CheckMate 214; NCT02231749), first-line nivolumab plus ipilimumab demonstrated significant overall survival improvements in patients with advanced/metastatic RCC, with a manageable safety profile. These findings indicate a potential for improved clinical outcomes in the early-stage adjuvant RCC setting.[4] Combining immunotherapies such as anti–PD-1 and anti–CTLA-4 agents, which target complementary pathways in the cancer-immunity cycle, might result in additive or synergistic antitumor activity compared with single-agent therapy.[5]

If licensed, nivolumab in combination with ipilimumab would offer an adjuvant treatment option for adult patients with localised RCC who have undergone partial or radical nephrectomy.

Regulatory & Development Status

Nivolumab, as a monotherapy and in combination, has Marketing Authorisation in the EU/UK for the following indications:[2]

- Melanoma
- Adjuvant treatment of melanoma
- Non-small cell lung cancer (NSCLC)
- Malignant pleural mesothelioma (MPM)
- Renal cell carcinoma (RCC)
- Classical Hodgkin lymphoma (cHL)

- Squamous cell cancer of the head and neck (SCCHN)
- Urothelial carcinoma
- Adjuvant treatment of urothelial carcinoma
- Mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H) colorectal cancer (CRC)
- Oesophageal squamous cell carcinoma (OSCC)
- Adjuvant treatment of oesophageal or gastro-oesophageal junction cancer (OC or GEJC)
- Gastric, gastro-oesophageal junction (GEJ) or oesophageal adenocarcinoma

Ipilimumab, as a monotherapy and in combination, has Marketing Authorisation in the EU/UK for the following indications:[3]

- Melanoma
- RCC
- NSCLC
- MPM
- dMMR or MSI-H CRC
- OSCC

The combination of nivolumab with ipilimumab is in phase II and III trials for several indications, some of which include:[6]

- NSCLC
- Melanoma
- Gastric cancer
- Hepatocellular carcinoma
- Glioblastoma
- Squamous Cell Carcinoma of the Head and Neck

Patient Group

Disease Area and Clinical Need

RCC (the most common type of kidney cancer in adults) is a disease in which malignant (cancer) cells are found in the lining of tubules (very small tubes) in the kidney.[7] The cells can grow into surrounding tissues or organs and may spread to other areas of the body.[8] Stage I, II, and III RCCs are referred to as localised RCCs, meaning the cancer is either completely inside the kidney or has grown into surrounding tissues but has not spread to another part of the body.[9,10] RCC usually affects people in their 60s and 70s and is rare in people under 50. Risk factors for RCC include obesity, smoking, high blood pressure, family history/genetics and long-term kidney dialysis. Many patients remain symptomless until later in disease course, but patients may experience lower back pain, lump or swelling on the side, blood in urine, fatigue, loss of appetite, high blood pressure, night sweats, swollen glands, bone pain, coughing up blood and swelling of the testicles in males.[11,12]

The age-standardised incidence rate of malignant neoplasm of kidney (ICD10 C64) is 23.7 in males and 12.7 in females per 100,000 population of newly diagnosed cases of cancer in England (data from 2017).[13] 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] Kidney cancer has a 79.3% 1-year and 63.8% 5-year age standardised survival rate.[15] In England, in 2020-21, there were 20,380 finished consultant episodes (FCE) and 17,908 admissions for malignant neoplasm of kidney, except renal pelvis (ICD-10 code C64) which resulted in 9,984 day-cases and 38,608 FCE bed days.[16]

Recommended Treatment Options

The main treatments for RCC include: [11]

- surgery to remove part or all of the affected kidney – this is the main treatment for most people
- cryotherapy or radiofrequency ablation – where the cancerous cells are destroyed by freezing or heating
- biological therapies – medicines that help stop the cancer growing or spreading
- embolisation – a procedure to cut off the blood supply to the cancer
- radiotherapy

There are currently no NICE recommended adjuvant treatments for RCC.

Clinical Trial Information

Trial	**CheckMate 914**; NCT03138512; 2016-004502-34; A Phase 3 Randomized, Double-Blind Study of Nivolumab Monotherapy or Nivolumab Combined With Ipilimumab vs Placebo in Participants With Localized Renal Cell Carcinoma Who Underwent Radical or Partial Nephrectomy and Who Are at High Risk of Relapse **Phase III** – Active, not recruiting **Location(s):** UK, 10 EU countries, USA, Canada and other countries **Primary completion date**: July 2024
Trial Design	Randomised, parallel assignment, quadruple blinded, placebo controlled
Population	N=1641; aged 18 years and older; patients with kidney tumour that has been completely resected, with no evidence of residual disease or distant metastases after nephrectomy
Intervention(s)	• Nivolumab • Ipilimumab
Comparator(s)	Matched placebo
Outcome(s)	Primary outcome measure: Disease-free survival (DFS) as assessed by BICR (Part A and Part B) [Time frame: Up to 10 years] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Nivolumab is already marketed in the UK as follows:[17]

- 100mg/10ml concentrate for solution for infusion (1 vial) costs £1097.00
- 120mg/12ml concentrate for solution for infusion (1 vial) costs £1,317.00
- 240mg/24ml concentrate for solution for infusion (1 vial) costs £2,633.00
- 40mg/4ml concentrate for solution for infusion (1 vial) costs £439.00

Ipilimumab is already marketed in the UK as follows:[18]

- 200mg/40ml concentrate for solution for infusion (1 vial) costs £15,000.00
- 50mg/10ml concentrate for solution for infusion (1 vial) costs £3,750.00

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Nivolumab for neoadjuvant and adjuvant treatment of localised renal cell carcinoma [ID4047]. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Pembrolizumab for adjuvant treatment of renal cell carcinoma [ID3810]. Expected July 2022.
- 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. Percutaneous radiofrequency ablation for renal cancer (IPG353). July 2010.
- NICE interventional procedure guidance. Laparoscopic partial nephrectomy (IPG151). January 2006.
- NICE interventional procedure. Laparoscopic nephrectomy (including nephroureterectomy) (IPG136). August 2005.

NHS England (Policy/Commissioning) Guidance

- NHS England. Specialised kidney, bladder and prostate cancer services (adults); Service specification. 170114S. February 2019
- 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: Radiotherapy (All ages). Service specification. B01/S/a

Other Guidance

- The European Association of Urology (EAU). Renal Cell Cancer (RCC) Guidelines (2021).[19]
- European Society for Medical Oncology (ESMO). Renal Cell Carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up (2019).[20]

Additional Information

References

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