Health Technology Briefing
February 2024

Nivolumab for treating advanced clear cell renal cell carcinoma after systemic treatment

Company/Developer	Bristol-Myers Squibb Pharmaceuticals Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 31387	NICE ID: Not available	UKPS ID: 672705

Licensing and Market Availability Plans

Currently in phase III clinical trial.

Summary

Subcutaneous (SC) Nivolumab is currently in clinical development for treating advanced or metastatic clear cell renal cell carcinoma (ccRCC) in adult patients who previously received systemic treatment. Metastatic cancer is when cancer cells have spread to other parts of the body and advanced cancer is when the cancer cannot be cured. ccRCC is the most common type of kidney cancer and is called as such because the cancer cells appear clear when viewed under a microscope. Most patients with renal cell carcinomas (RCC) are usually asymptomatic in the early stage, but symptoms, which include blood in the urine, pain in lower back or side, weight loss and tiredness, appear as the cancer progresses.

Nivolumab is a type of protein (a monoclonal antibody) designed to recognise and bind to a protein called programmed death-1 (PD-1), which is present on the surface of many cancer cells and reduces the immune system's ability to attack cancer cells. Nivolumab therefore increases the body's ability to kill cancer cells and slow down progression of the disease. Subcutaneous (SC) nivolumab is an alternative for intravenous (IV) infusion reducing the need for IV ports, thereby lowering the risk of associated complications such as infections and phlebitis. The SC formulation also decreases the time for dose preparation and administration. If licensed, SC nivolumab would offer an additional treatment option for adult patients with metastatic ccRCC who have previously received systemic treatment.

Proposed Indication

Treatment of advanced or metastatic clear cell renal cell carcinoma (ccRCC) in adult patients who have received prior systemic therapy.[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 programmed death ligands (PD-L) PD-L1 and PD-L2. Engagement of PD-1 with 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]

Subcutaneous (SC) nivolumab (BMS-986298) is currently in clinical development for treating advanced or metastatic ccRCC in adult patients who have received prior systemic therapy. In the phase III clinical trial (CheckMate-67T, NCT04810078), patients received a specific dose of SC nivolumab on specific days.[1]

Key Innovation

As an alternative to intravenous (IV) infusion, SC nivolumab alleviates the need for IV ports, thereby lowering the risk of associated complications such as infections and phlebitis.[3] The SC formulation also reduces the time for dose preparation and administration, which may decrease overall treatment burden and reduce patient time in the clinic.[3] If licensed, SC nivolumab would offer an additional treatment option for previously treated advanced or metastatic ccRCC that reduces dose preparation and administration times, and the risk of complications associated with IV administration.[3]

Regulatory Development Status

SC nivolumab does not currently have marketing authorisation in the EU/UK for any indication.

IV nivolumab is currently marketed in the EU/UK in combination with other technologies for the following indications:[4]

- Advanced (unresectable or metastatic) melanoma in adults and adolescents
- First-line treatment of metastatic non-small cell lung cancer (NSCLC) in adults whose tumours have no sensitising EGFR mutation or ALK translocation
- Neoadjuvant treatment of resectable (tumours ≥ 4cm or node positive) NSCLC in adults
- First-line treatment of adults with unresectable malignant pleural mesothelioma
- First-line treatment of adults with intermediate/poor-risk advanced renal cell carcinoma (RCC)
- First-line treatment of adults with advanced RCC
- Treatment of adults with mismatch repair deficient or microsatellite instability-high metastatic colorectal cancer prior to fluoropyrimidine-based combination chemotherapy
- First-line treatment of adults with unresectable advanced, recurrent or metastatic oesophageal squamous cell carcinoma (OSCC) with tumour cell PD-L1 expression ≥ 1%
- First-line treatment of adults with HER2-negative advanced or metastatic gastric, gastro-oesophageal junction or oesophageal adenocarcinoma whose tumours express PD-L1 with a combined positive score ≥ 5

IV nivolumab is also currently marketed in the EU/UK as a monotherapy for the following indications: [4]

- Adjuvant treatment of adults and adolescents with stage IIB or IIC melanoma, or melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection
- Treatment of locally advanced NSCLC after prior chemotherapy in adults
- Treatment of advanced RCC after prior therapy in adults
- Treatment of adults with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant and treatment with brentuximab vedotin
- Treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy
- Treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy
- Adjuvant treatment of adults with muscle invasive urothelial carcinoma with tumour cell PD-L1 expression ≥ 1%, who are at high risk of recurrence after undergoing radical resection
- Treatment of adults with unresectable advanced, recurrent or metastatic Oesophageal squamous cell carcinoma (OSCC) after prior fluoropyrimidine- and platinum-based combination chemotherapy

SC nivolumab is currently in phase III/II clinical development for:[5]

- Melanoma
- Neoplasms by site
- Lung cancer
- Colorectal cancer
- Pancreatic ductal adenocarcinoma
- Ovarian cancer

Patient Group

Disease Area and Clinical Need

Clear cell renal cell carcinoma is the most common type of kidney cancer in adults. In RCC, cancer starts in cells in one of the nephrons inside the kidney. Nephrons filter the blood and make urine. Around 80% of kidney cancers are RCC. There are different types of RCC. The main types are: clear cell (between 70% and 80% of RCCs), papillary (between 5% and 10% of RCCs) and chromophobe (between 3% and 5% of RCCs).[6] When the tumour is viewed under the microscope, the tumour cells look clear, that is why the ccRCC is named as such.[7] Metastatic RCC is when the cancer has spread to other parts of body.[6] Advanced cancer is most often used to describe cancers that cannot be cured.[8]

Early stages of RCC are often asymptomatic, however symptoms can include blood in urine (haematuria), pain in lower back or side, high blood pressure (hypertension), loss of appetite and weight, bone pain, breathing difficulties, tiredness, high temperature, night sweats, swollen neck glands, and coughing up blood.[9] Risk factors for RCC include: smoking, kidney disease, being overweight, faulty genes and inherited conditions, and family history of kidney cancer.[10]

In England in 2022-2023, there were 29,076 finished consultation episodes (FCE) for malignant neoplasm of kidney, except renal pelvis (ICD-10 code C64), resulting in 16,963 day cases and 49,389 FCE bed days.[11] There are around 4,700 kidney cancer deaths in the UK every year (2017-2019). Incidence rates for kidney cancer in the UK are highest in people aged 85 to 89 years (2016-2018).[12]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends the following targeted treatment options for previously treated advanced RCC:[13-17]

- Axitinib (oral)

- Nivolumab (IV)
- Everolimus (oral)
- Cabozantinib (oral)
- Lenvatinib with everolimus (oral)

Clinical Trial Information

Trial	**CheckMate-67T; NCT04810078; 2020-003655-15;** A Phase 3, Open-label, Randomized, Noninferiority Trial of Subcutaneous Formulation of Nivolumab Versus Intravenous Nivolumab in Participants With Advanced or Metastatic Clear Cell Renal Cell Carcinoma Who Have Received Prior Systemic Therapy **Phase III -** Active, not recruiting **Location(s):** 9 EU countries, USA, and other countries
Trial Design	Randomized, parallel assignment, quadruple
Population	N=632 (estimated); Participants aged 18 years and older with advanced or metastatic ccRCC who have received prior systemic therapy
Intervention(s)	Nivolumab (SC)
Comparator(s)	Nivolumab (IV)
Outcome(s)	Primary outcome measures: • Time-averaged serum concentration over 28 days [Time Frame: Up to 28 days] • Trough serum concentration at steady-state [Time Frame: Up to 4 months] See trial record for full list of other outcomes.
Results (efficacy)	SC nivolumab demonstrated noninferiority of Cavgd28 (time-averaged Opdivo serum concentration over 28 days) and Cminss (trough serum concentration at steady state) compared to IV nivolumab, the study's co-primary endpoints. Additionally, SC nivolumab showed a noninferior objective response rate (ORR) as assessed by Blinded Independent Central Review (BICR) vs. IV nivolumab, a key secondary endpoint.[18]
Results (safety)	The safety profile of SC nivolumab was consistent with the IV formulation.[18]

Estimated Cost

The cost of SC nivolumab is not yet known.

The NHS indicative price for nivolumab as IV infusion is:[19]

- For 100mg/10ml concentrate for solution for infusion vials £1,097.00
- For 120mg/12ml concentrate for solution for infusion vials £1,317.00
- For 240mg/24ml concentrate for solution for infusion vials £2,633.00
- For 40mg/4ml concentrate for solution for infusion vials £439.00

Relevant Guidance

NICE Guidance

- NICE technology appraisal guidance in development. Belzutifan for previously treated advanced renal cell carcinoma (GID-TA11086). Expected date of issue to be confirmed.
- NICE technology appraisal guidance in development. Atezolizumab for adjuvant treatment of renal cell carcinoma with a high risk of metastasis (GID-TA11000). Expected date of issue to be confirmed.
- NICE technology appraisal guidance. Tivozanib for treating advanced renal cell carcinoma (TA512). March 2018.
- NICE technology appraisal guidance. Cabozantinib for previously treated advanced renal cell carcinoma (TA463). August 2017.
- NICE interventional procedures guidance. Irreversible electroporation for treating renal cancer (IPG443). February 2013.
- NICE interventional procedures guidance. Laparoscopic cryotherapy for renal cancer (IPG405). August 2011.
- NICE interventional procedures guidance. Percutaneous cryotherapy for renal cancer (IPG402). July 2011.
- NICE pathways pilot. Renal cell carcinoma (GID-TA11186). Expected date of publication to be confirmed.

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

Other Guidance

- European Association of Urology (EAU). EUA Guidelines on Renal Cell Carcinoma. March 2023.[20]
- European Society for Medical Oncology (ESMO). eUpdate – Renal Cell Carcinoma Treatment Recommendations. September 2021.[21]
- ESMO. Renal cell carcinoma: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. May 2019.[22]

Additional Information

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