Innovation Observatory

NHS National Institute for Health Research

HEALTH TECHNOLOGY BRIEFING APRIL 2019

Nivolumab in combination with cabozantinib for metastatic renal cell carcinoma – first-line

NIHRIO ID	18319	**NICE ID**	10039
Developer/Company	Bristol-Myers Squibb	**UKPS ID**	646339

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

SUMMARY

Nivolumab in combination with cabozantinib is in development for first-line treatment of metastatic renal cell carcinoma (mRCC). Renal cell carcinoma 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 quite late, and tend to spread to other organs quite early. There are many types of RCCs and each type is derived from a different cell lineage and has its own distinct characteristics. In mRCC, the tumour has spread beyond the regional lymph nodes to other parts of the body.

Nivolumab works by improving the activity of white blood cells thereby increasing the ability of the immune system to kill cancer cells. Cabozantinib works to stop signals that cancer cells use to divide and grow. It is thought that when used in combination, both drugs may be more effective than each drug on its own. If licenced, nivolumab in combination with cabozantinib may improve long-term outcomes in mRCC patients who currently have limited treatment options.

PROPOSED INDICATION

Metastatic renal cell carcinoma (mRCC) – first line[a]

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 the ligands PD-L1 and PD-L2. The PD-1 receptor is a negative regulator of T-cell activity that has been shown to be involved in the control of T-cell immune responses. 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 ligands.[1]

Cabozantinib (Cabometyx; XL-184) is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) implicated in tumour growth and angiogenesis, pathologic bone remodelling, drug resistance, and metastatic progression of cancer. Cabozantinib was evaluated for its inhibitory activity against a variety of kinases and was identified as an inhibitor of MET (hepatocyte growth factor receptor protein) and VEGF (vascular endothelial growth factor) receptors. In addition, cabozantinib inhibits other tyrosine kinases including the GAS6 receptor (AXL), RET, ROS1, TYRO3, MER, the stem cell factor receptor (KIT), TRKB, Fms-like tyrosine kinase-3 (FLT3), and TIE-2.[2]

Nivolumab in combination with cabozantinib is in development for mRCC. In the phase III clinical trial (NCT03141177; CheckMate 9ER) subjects receive nivolumab and cabozantinib as specified dose on specified days. Dosing specifics and duration of treatment were not reported on the trial registry.[3,4]

INNOVATION AND/OR ADVANTAGES

Over the past decade, treatment options for advanced RCC have evolved to include multiple agents targeting the VEGF pathway. In addition, the recent innovation of treating cancer with immunotherapy has further expanded the therapeutic armamentarium. Biomarker studies suggest that promotion of an immune suppressive tumour microenvironment can contribute to anti-VEGF therapy resistance and point to a rationale for combining anti-VEGF therapy with immunotherapy. Cabozantinib, a tyrosine kinase inhibitor with targets including VEGF receptor, MET and the TAM receptor family has shown immunomodulatory properties suggestive of synergistic effects with immune checkpoint inhibitors. A recent phase I study combination of the PD-1 inhibitor nivolumab with cabozantinib showed encouraging antitumor activity in pre-treated patients with mRCC and other advanced genitourinary tumours.[5,6]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Nivolumab in combination with cabozantinib does not currently have Marketing Authorisation in the EU/UK for any indication.

[a] Information provided by Bristol-Myers Squibb on UK PharmaScan

Nivolumab in combination with cabozantinib is currently in phase III clinical development for the treatment of clear cell renal cell carcinoma and in phase II clinical development for the treatment of various types of cancers including breast, non-clear cell renal cell carcinoma, hepatocellular carcinoma, bladder small cell carcinoma and others.[7]

PATIENT GROUP

DISEASE BACKGROUND

Renal cell carcinoma (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.[8]

Several factors increase a person's risk of developing RCC including age, genetics, family history, and exposure to other risk factors (including some potentially avoidable lifestyle factors). Lifestyle factors such as smoking increases risk by 33%. Radiotherapy for cancers, certain occupational exposures, certain medical conditions such as thyroid cancer, high blood pressure, and diabetes and inadequate physical activity may also relate to higher RCC risk.[9]

At present, the majority of RCCs are found incidentally from abdominal ultrasound or computer tomography examinations undertaken for various reasons. RCC can become very large without any symptoms, due to the retroperitoneal position of the kidney. 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.[10]

Patients with RCC can present with a range of symptoms; unfortunately, many patients are asymptomatic until the disease is advanced. At presentation, approximately 25% of individuals either have distant metastases or advanced loco regional disease.[11] The American Joint Committee on Cancer (AJCC) tumour node metastases (TNM) system is used to grade RCC into stages I to IV. mRCC, in which the tumour has spread beyond the regional lymph nodes to other parts of the body, is generally defined as stage IV.[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 was the seventh most common cancer in the UK in 2015. The definition of kidney cancer includes cancers of the renal parenchyma (90%), the renal pelvis and the ureter. Cancers of the renal parenchyma are also known as RCCs.[14]

The incidence of kidney cancer was 12,547 new cases in England and Wales in 2015 with more than 4 in 10 cases diagnosed at a late stage in England (2014). Around 7,900 of these new cases were in males making it the 6th most common cancer in males. 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. An estimated 46,800 people who had previously been diagnosed with kidney cancer were alive in the UK at the end of 2010.[15]

In 2016, kidney cancer was the 13th most common cause of cancer death in the UK accounting for 3% of all cancer deaths. Data from 2010-2011 show 6 in 10 (56%) people diagnosed with kidney cancer in England and Wales survive their disease for five years or more while about half (50%) survive their

disease for ten years or more. 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. People diagnosed at stage IV died at more than twice the rate of the general population. Data from 2014-2016 estimate approximately 4,500 kidney cancer deaths in the UK every year.[15,16]

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.[14] Hospital admissions data for England in 2017-2018 recorded 20,654 finished consultant episodes (FCE) for malignant neoplasm of kidney, except renal pelvis (ICD 10: C64), 17,520 hospital admissions and 8,170 day cases.[17]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

There are currently no treatments that reliably cure advanced and/or mRCC. The primary objectives of medical intervention are relief of physical symptoms and maintenance of function.[12]

Metastasectomy and other local treatment strategies including whole-brain radiotherapy, conventional radiotherapy (RT), stereotactic radiosurgery, stereotactic body radiotherapy, CyberKnife® RT and hypofractionated RT can be considered and carried out for selected patients after multidisciplinary review.[18]

CURRENT TREATMENT OPTIONS

The following treatment options for first-line mRCC are recommended by NICE:[19]

- Sunitinib is recommended as a first-line treatment option for people with advanced and/or mRCC who are suitable for immunotherapy and have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.

- Bevacizumab, sorafenib and temsirolimus are **not recommended** as first-line treatment options for people with advanced and/or mRCC. People who are currently being treated with bevacizumab (first-line), sorafenib (first- and second-line), sunitinib (second-line) and temsirolimus (first-line) for advanced and/or metastatic renal cell carcinoma should have the option to continue their therapy until they and their clinicians consider it appropriate to stop.

PLACE OF TECHNOLOGY

If licensed, nivolumab in combination with cabozantinib will offer an additional treatment option for mRCC patients who currently have few well-tolerated effective therapies available.

CLINICAL TRIAL INFORMATION

Trial	**Checkmate 9ER, NCT03141177, EudraCT2017-000759-20; nivolumab in combination with cabozantinib vs. sunitinib; phase III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing

Source of Information	Trial registry[3,4], abstract[5]
Location	EU (incl UK), USA, and other countries
Design	Randomised, parallel assignment, open-label
Participants	n=630 (planned); age ⩾18 years; RCC with a clear-cell component; advanced or metastatic (AJCC stage IV) RCC; no prior systemic therapy for RCC (exception - one prior adjuvant or neoadjuvant therapy for completely resectable RCC if such therapy did not include an agent that targets VEGF or VEGF receptors and if recurrence occurred at least 6 months after the last dose of adjuvant or neoadjuvant therapy)
Schedule	Patients are assigned to either the experimental doublet arm or active comparator monotherapy arm, with a specified dose on specified days: **Arm A: Nivolumab + cabozantinib** **Arm B: Sunitinib** An experimental triple arm (nivolumab, ipilimumab, cabozantinib) was discontinued by protocol amendment.
Follow-up	Treatment will continue until disease progression or unacceptable toxicity (maximum nivolumab treatment of 2 years). After the patients discontinue from study therapy there will be 2 follow up visits in the next 100 days. After the follow-up 2 visit, all participants will be followed for overall survival status every 3 months (+/- 14 days) until death, withdrawal of consent, loss to follow-up, or end of study.
Primary Outcomes	Progression Free Survival (PFS) per blinded independent central review (BICR) [Time Frame: Up to 21 months]
Secondary Outcomes	• Overall Survival (OS) [Time Frame: Up to 64 months] • Objective Response Rate (ORR) [Time Frame: Approximately 16 months] • Incidence of adverse events (AEs) [Time Frame: Up to 64 months] • Incidence of Serious Adverse Events (SAEs) [Time Frame: Up to 64 months]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated study completion date reported as Apr 2023.

ESTIMATED COST

Nivolumab (Opdivo) is already marketed in the UK; a 100mg/10mL concentrate for solution for infusion vial costs £1,097, a 240mg/24mL concentrate for solution for infusion vial costs £2,633, and a 40mg/4ml concentrate for solution for infusion vial costs £439.[20]

Cabozantinib (Cabometyx) is already marketed in the UK; 30 x 20, 40, or 60 mg cabozantinib (as cabozantinib s-malate) tablets costs £5143.00.[21]

ADDITIONAL INFORMATION

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal in development. Avelumab with axitinib for untreated advanced or metastatic renal cell carcinoma [ID1547]. Expected publication date to be confirmed.
- NICE technology appraisal in development. Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]. Expected publication 27 May 2020.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated metastatic renal cell carcinoma [ID1182]. Expected publication May 2019.
- 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.

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. 2019[18]
- NICE cancer service guideline. Improving outcomes in urological cancers (CSG2). 2002[22]

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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.