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HEALTH TECHNOLOGY BRIEFING
AUGUST 2019

Nivolumab for high risk invasive urothelial carcinoma - adjuvant

Developer/Company	12497	**NICE ID**	9499
	Bristol-Myers Squibb Pharmaceuticals Ltd	**UKPS ID**	641507

Licensing and market availability plans	Currently in pre-registration

SUMMARY

Nivolumab is in development for the treatment of a type of bladder cancer that is at high risk of spreading beyond the lining of the bladder into the surrounding muscle. Bladder cancer starts when cells that make up the urinary bladder start to grow out of control. As more cancer cells develop, they can form a tumour and, with time, spread to other parts of the body. Urothelial cancer is the most common type of bladder cancer. High risk invasive urothelial cancer is when there is a greater chance for the cancer cells spreading to the lymph glands around the bladder and therefore patients have a reduced chance of cure.

Nivolumab, is a monoclonal antibody, a type of protein that has been designed to recognise and attach to a receptor (target) called PD-1 found on certain cells of the immune system called T cells. Cancer cells can produce proteins (PD-L1 and PD-L2) that attach to this receptor and switch off the activity of the T cells, preventing them from attacking the cancer. By attaching to the receptor, nivolumab prevents PD-L1 and PD-L2 from switching off the T cells, thereby increasing the ability of the immune system to kill cancer cells. If licenced for the adjuvant treatment of high risk invasive urothelial carcinoma, nivolumab has the potential to increase the length of time until the cancer comes back.

PROPOSED INDICATION

Adjuvant treatment of invasive urothelial cancer at high risk of recurrence originating in the bladder, ureter, or renal pelvis following radical surgical resection.[a,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 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.[2]

Nivolumab is at phase III clinical development (NCT02632409) as an adjuvant therapy for patients who have undergone radical surgery for invasive urothelial cancer. Treatment regimen is not specified.[1]

INNOVATION AND/OR ADVANTAGES

Urothelial carcinoma of the ureter or renal pelvis is typically managed with nephroureterectomy, but despite surgery with or without neo/adjuvant chemotherapy many patients with invasive urothelial carcinoma are at high risk of recurrence and death. Nivolumab is a PD-1 inhibitor that has proven efficacious for metastatic or unresectable urothelial carcinoma progressing despite chemotherapy.[3] The company aims to extend the licenced use of nivolumab in the metastatic population to the adjuvant setting in patients with high risk invasive urothelial cancer prior to the cancer becoming metastatic The nature of this SPC amendment is classed as a Type II variation.[a]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

In the UK, Nivolumab as monotherapy or in combination with other cancer therapies has the following therapeutic indications:[2]

- Melanoma: as monotherapy or in combination with ipilimumab is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults.
- Adjuvant treatment of melanoma: as monotherapy is indicated for the adjuvant treatment of adults with melanoma with involvement of lymph nodes or metastatic disease who have undergone complete resection.
- Non-Small Cell Lung Cancer (NSCLC): as monotherapy is indicated for the treatment of locally advanced or metastatic non-small cell lung cancer after prior chemotherapy in adults.
- Renal Cell Carcinoma (RCC): as monotherapy is indicated for the treatment of advanced renal cell carcinoma after prior therapy in adults. In combination with ipilimumab is indicated for

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

the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.

- Classical Hodgkin Lymphoma (cHL): as monotherapy is indicated for the treatment of adult patients with relapsed or refractory classical Hodgkin lymphoma after autologous stem cell transplant (ASCT) and treatment with brentuximab vedotin.

- Squamous Cell Cancer of the Head and Neck (SCCHN): as monotherapy is indicated for the treatment of recurrent or metastatic squamous cell cancer of the head and neck in adults progressing on or after platinum-based therapy.

- Urothelial Carcinoma: as monotherapy is indicated for the treatment of locally advanced unresectable or metastatic urothelial carcinoma in adults after failure of prior platinum-containing therapy.

The most common side effects with nivolumab (which may affect more than 1 in 10 people) include tiredness, diarrhoea, nausea (feeling sick), rash and itching, pain in joints, muscles and bones, and hypothyroidism (an underactive thyroid gland), most of which are mild to moderate in severity. Other common side effects with Opdivo in combination with ipilimumab, which are also mostly mild or moderate, include pyrexia (fever), thyroid issues, decreased appetite, vomiting, colitis (inflammation of the gut), abdominal (belly) pain, headache and breathing difficulty. Nivolumab is also commonly associated with side effects related to the activity of the immune system on body organs. Most will go away with appropriate treatment or on stopping nivolumab.[4]

Nivolumab as monotherapy or in combination with other medicinal products is at phase III clinical trial or pre-registration for several types of cancers including glioblastoma, hepatocellular carcinoma, renal cell carcinoma and Hodgkin's lymphoma.[5]

PATIENT GROUP

DISEASE BACKGROUND

Urothelial (previously known as transitional cell) carcinoma is the predominant histologic type of bladder cancer in the United States and Western Europe.[6] Around 90% of new bladder cancers diagnosed in the UK are urothelial cancer.[7,8] Early urothelial cancer (non-muscle-invasive) affects only the inner lining of the bladder (urothelium), but in advanced urothelial cancer the cancer has grown into deeper layers including connective tissue or muscle (invasive).[8,9] Metastatic urothelial cancer occurs when the cancer has spread to other parts of the body, such as the liver or bones.[10]

Urothelial cancer usually takes a long time to develop, and is most common in people over 60 years old. It is also more common in men than women, but this may be because more men have smoked or been exposed to chemicals at work in recent decades.[11] Studies of urothelial bladder cancer have identified multiple risk factors, the most important of which are cigarette smoking and various occupational exposures.[6] The main symptom of urothelial cancer is blood in the urine. Other symptoms may include urinary frequency or urgency, whilst symptoms of metastatic urothelial cancer include loss of appetite, weight loss or change in bladder habits, pelvic pain, bone pain, and swelling of the legs.[12,13]

CLINICAL NEED AND BURDEN OF DISEASE

In the UK in 2016, bladder cancer was the 10th most common cancer accounting for 3% of all new cancer cases.[14] In England in 2017 there were a total of 8,686 newly diagnosed cases of bladder cancer

(ICD-10 code C67) registered, of which 6,327 were in men.[15] The European age-standardised incidence rate of bladder cancer in the UK is projected to decrease by 34% in the UK by 2035 from 20.44 per 100,000 in 2014 (equating to 10,057 observed cases) to 13.43 per 100,000 (equating to 10,386 projected cases).[16] This trend has been observed in the UK since the 1990s, with an observed decrease of about two-fifths (41%).[14]

In 2016, bladder cancer was the 9th most common cause of cancer death in the UK, accounting for 3% of all cancer deaths.[14] In 2017, in England and Wales there were a total of 5,014 deaths registered due to bladder cancer (ICD-10 code C67).[17] For the UK, the European age-standardised mortality rate is projected to decrease from 10.91 per 100,000 (equating to 5,369 observed cases) in 2014 to 9.39 per 100,000 (equating to 7,771 projected cases) by 2035.[18]

The age-standardised 1-year and 5–year survival for persons diagnosed with bladder cancer in England in 2017 was 74.8% and 55.1% respectively.[19]

The Hospital Episodes Statistics (HES) data for England in 2017-18 of admitted patients with primary diagnosis malignant neoplasm of the renal pelvis, malignant neoplasm of the ureter and malignant neoplasm of the bladder (ICD-10 codes C65, C66 and C67 respectively) recorded a total of 77,868 finished consultant episodes (FCEs), 72,730 admissions and 41,941 day cases .[20]

HES data for procedures undertaken in English hospitals between 2017 and 2018 reported a total of 501 FCEs and 485 admissions for primary procedure cystectomy, other specified total excision of bladder and unspecified total excision of bladder (OPCS-4 codes M343, M348 and M349). OPCS-4 codes reported as agreed for the Specialised kidney, bladder and prostate cancer services (Adults), NHS England.[21,22]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

In England, for people diagnosed with invasive bladder cancer, NICE recommends that a specialist urology multidisciplinary team reviews all cases of muscle-invasive bladder cancer, to offer a choice of radical cystectomy or radiotherapy with a radiosensitiser to people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable. Ensure that the choice is based on a full discussion between the person and an urologist who performs radical cystectomy, a clinical oncologist and a clinical nurse specialist. Offer neoadjuvant chemotherapy using a cisplatin combination regimen before radical cystectomy or radical radiotherapy to people with newly diagnosed muscle-invasive urothelial bladder cancer for whom cisplatin-based chemotherapy is suitable. Ensure that they have an opportunity to discuss the risks and benefits with an oncologist who treats bladder cancer. After radical cystectomy, those patients for whom neoadjuvant chemotherapy was not suitable (because muscle invasion was not shown on biopsies before cystectomy) may be offered cisplatin adjuvant combination chemotherapy.[23]

CURRENT TREATMENT OPTIONS

According to the current NICE treatment pathway for patients with invasive urothelial cancer, cisplatin combination chemotherapy maybe be offered as adjuvant treatment after radical cystectomy for whom neoadjuvant chemotherapy was not suitable.[23] In patients who have received radical cystectomy, but are not eligible for adjuvant cisplatin-based chemotherapy (according to the European Association of Urology over 50% of patients with urothelial cancer are likely not eligible for

cisplatin-based chemotherapy),[24] a watchful-waiting (observation) approach is taken until disease recurrence.[23]

PLACE OF TECHNOLOGY

If licenced, adjuvant treatment with nivolumab in people with high risk invasive urothelial cancer will present an additional treatment option for this population that currently have limited treatment options and that are at high risk of their cancers spreading.

CLINICAL TRIAL INFORMATION

Trial	**CheckMate 274, NCT02632409, EudraCT-2014-003626-40; adults 18 years old and over; adjuvant nivolumab vs placebo; phase III**
Sponsor	Bristol-Myers Squibb
Status	Ongoing
Source of Information	Trial registry[1]
Location	EU (incl UK), USA, Canada and other countries.
Design	Randomised, placebo-controlled
Participants	n=700 (planned); aged 18 year and older; invasive urothelial cancer at high risk of recurrence originating in the bladder, ureter, or renal pelvis; have had radical surgical resection (e.g. radical cystectomy), performed within the last 120 days
Schedule	Randomised to nivolumab (240 mg every 2 weeks IV)[b] or placebo (dose not specified)
Follow-up	Follow up to 5 years
Primary Outcomes	Disease free survival (DFS) [Time Frame: Approximately 5 years after the first subject is randomized]
Secondary Outcomes	Overall survival (OS) [time frame: Approximately 5 years after the first subject is randomized] Non-Urothelial track recurrence free survival (NUTRFS) [time frame: Approximately 5 years after the first subject is randomized] Disease specific survival (DSS) [time frame: Approximately 5 years after the first subject is randomized]
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Primary completion date reported as November 2020 Estimated final study completion date: November 2026[b]

[b] Information provided by Bristol-Myers Squibb Pharmaceuticals Ltd

ESTIMATED COST

The NHS indicative price for nivolumab (Opdivo) 100mg/10ml, 240mg/24ml and 40mg/4ml concentrate for solution for infusion vials is £1,097.00, £2,633.00 and £439.00 respectively.[25]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS06). December 2015.

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

OTHER GUIDANCE

- European Association of Urology. Guidelines on muscle-invasive and metastatic bladder cancer. 2018.[26]
- NHS England. Guidelines for the management of bladder cancer. 2016.[27]
- ESMO bladder cancer practice guidelines for diagnosis, treatment and follow-up. 2014.[28]

ADDITIONAL INFORMATION

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