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HEALTH TECHNOLOGY BRIEFING NOVEMBER 2019

Avelumab in addition to best supportive care for locally advanced or metastatic urothelial cancer

NIHRIO ID	11976	**NICE ID**	10112
Developer/Company	Merck Serono Ltd	**UKPS ID**	644772

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

SUMMARY

Avelumab in addition to best supportive care (BSC) is in clinical development for the maintenance treatments of adults with locally advanced or metastatic urothelial cancer that did not progress on or following completion of first-line chemotherapy. Urothelial cancer occurs on the lining of the bladder and other parts of the urinary system. In advanced urothelial cancer, cancer has grown into deeper layers including connective tissue or muscle. Metastatic urothelial cancer is when the cancer has spread to other parts of the body, such as the liver or bones. Urothelial cancer usually occurs in patients aged 60 years and older, where patients may have other medical conditions or are not fit enough to be given certain treatments.

Avelumab administered by intravenous infusion is designed to stimulate the body's own immune system to fight cancer cells. If licensed, avelumab in addition to BSC will offer a maintenance treatment option for patients with locally advanced or metastatic urothelial cancer that did not progress during or following completion of first-line chemotherapy.

PROPOSED INDICATION

Maintenance therapy in adult patients with locally advanced or metastatic urothelial cancer that did not progress on or following completion of first-line chemotherapy.[1]

TECHNOLOGY

DESCRIPTION

Avelumab (Bavencio) is a human immunoglobulin G1 (IgG1) monoclonal antibody directed against programmed death-ligand 1 (PD-L1). Avelumab binds PD-L1 and blocks the interaction between PD-L1 and the programmed death 1 (PD-1) and B7.1 receptors. This removes the suppressive effects of PD-L1 on cytotoxic $CD8^+$ T-cells, resulting in the restoration of anti-tumour T-cell response. Avelumab has also shown to induce natural killer (NK) cell-mediated direct tumour cell lysis via antibody-dependent cell-mediated cytotoxicity (ADCC).[2]

Avelumab is in clinical development for the treatment of patients with locally advanced or metastatic (stage 4) urothelial cancer that did not progress on or after completion of first-line chemotherapy. In the phase III clinical trial (NCT02603432) participants will receive 10 milligram per kilogram (mg/kg) of avelumab as a 1-hour intravenous (IV) infusion once every 2 weeks (Q2W)[a] in 4-week cycles in addition to BSC as deemed appropriate by the treating physician, and could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc. BSC does not include any active anti-tumour therapy, however local radiotherapy of isolated lesions with palliative intent is acceptable.[1]

INNOVATION AND/OR ADVANTAGES

This is a new indication and line of treatment for avelumab in addition to best supportive care in this setting. Avelumab is not licensed for the treatment of urothelial cancer.[2] In a phase Ib trial, avelumab showed an objective response rate (ORR) of 18.2% in post-platinum metastatic urothelial carcinoma, with a tolerable safety profile (grade 3/4 adverse events, 6.8%).[3] Further avelumab has shown anti-tumour activity in the treatment of patients with platinum-refractory metastatic urothelial cancer and a manageable safety profile was reported in all avelumab treated patients.[4]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Avelumab is indicated in the EU/UK for the following:[2]

- As a monotherapy for the treatment of metastatic Merkel cell carcinoma.
- In combination with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC).

The most common side effects with avelumab used alone (which may affect more than 1 in 10 people) include tiredness, nausea, diarrhoea, decreased appetite, constipation, infusion-related reactions, weight loss and vomiting. Serious side effects include immune-related and infusion-related reactions, anaemia, difficulty breathing and abdominal pain.[5]

[a] Information provided by Merck Serono Ltd on UK PharmaScan

PATIENT GROUP

DISEASE BACKGROUND

Urothelial cancer (transitional cell carcinoma) occurs on the urothelium (the lining on the inside of the bladder, ureters and urethra and the renal pelvis). Around 90% of bladder cancers in the UK and urothelial cancer.[6] Early urothelial cancer (non-muscle-invasive) affects only the lining of the urothelium, but in advanced urothelial cancer grows into deeper layers including connective tissue or muscle. Metastatic urothelial cancer occurs when the cancer has spread to other parts of the body, such as the liver or bones.[7]

Urothelial cancer usually takes a long time to develop and is common in people over 60 years. 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.[8]

The main symptom of urothelial cancer is blood in the urine but symptoms may only appear once the cancer grows larger or into the deeper layers of the bladder wall for both men and women. Other symptoms may include urinary frequency or urgency, whilst symptoms of metastatic urothelial cancer include loss of appetite, weight loss or change in bowel habits.[9]

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.[10] In England in 2017, there were 8,686 registrations of newly diagnosed cases of malignant neoplasm of bladder (ICD-10 code C67) and the direct age-standardised rate per 100,000 population was 27.6 among males and 8.2 among females.[11] Bladder cancer incidence rates are projected to fall by 34% in the UK between 2014 and 2035, from 20.44 cases per 100,000 (10,057 observed cases) to 13.43 cases per 1 00,000 population by 2035 (10,386 projected cases).[12]

In England, in 2018-19 there were 73,789 finished consultant episodes (FCEs) for malignant neoplasm of the bladder (ICD-10 code C67), and 69,198 admissions resulting in 100,777 bed days and 41,236 day cases.[13]

In England in 2017, there were 5,014 deaths with malignant neoplasm of the bladder (ICD-10 code C67) recorded as the underlying cause.[14] The age-standardised 1-year and 5–year survival for persons diagnosed with bladder cancer in England in 2017 was 74.1% and 52.6% respectively.[15]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

For most patients with locally advanced urothelial cancer, the treatment aims to slow cancer and reduce symptoms.[16] Surgery (cystectomy) or radiotherapy on the bladder and lymph nodes may be used.[17] Chemotherapy may be given before or after surgery, before radiotherapy or during radiotherapy (chemoradiotherapy).[18]

For advanced or metastatic urothelial cancer, treatment may include chemotherapy to shrink cancer or keep it under control. Older patients who are less fit might find the side effects of intensive chemotherapy too severe, but is possible to have less intensive chemotherapy.[19] Radiotherapy may be offered if the cancer is causing symptoms such as pain; it will not cure cancer but can improve the quality of life and help to keep cancer under control.[20]

CURRENT TREATMENT OPTIONS

Currently NICE does not recommend any maintenance treatment option for patients with locally advanced or metastatic urothelial cancer that did not progress during or following completion of first-line chemotherapy.

PLACE OF TECHNOLOGY

If licensed, avelumab will offer a maintenance treatment option for patients with locally advanced or metastatic urothelial cancer that did not progress during or following completion of first-line chemotherapy.

CLINICAL TRIAL INFORMATION

Trial	**JAVELIN Bladder 100**, NCT02603432, **B9991001** EudraCT- 2015-003262-86; **adults ≥ 18 year; avelumab + best supportive care (BSC) vs BSC alone, phase III**
Sponsor	Pfizer
Status	Ongoing
Source of Information	Trial registry[1,21]
Location	EU (incl UK), USA, Canada and other countries
Design	Randomised, parallel assignment, open-label
Participants	n=700 (planned) aged ≥ 18 years; males or females; stage IV, unresectable locally advanced or metastatic transitional cell carcinoma of the urothelium, no evidence of progressive disease following completion of first-line chemotherapy

Schedule	Patients randomised to one of two arms:
	• Avelumab plus BSC
	  ○ Avelumab-1 hour intravenous infusion every 2 weeks (Q2W) in 4-week cycles
	  ○ BSC will be administered as deemed appropriate by the treating physician and could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc. BSC does not include any active anti-tumour therapy, however local radiotherapy of isolated lesions with palliative intent is acceptable.
	• BSC alone
	  ○ BSC will be administered as deemed appropriate by the treating physician and could include treatment with antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management (including palliative radiotherapy), etc. BSC does not include any active anti-tumour therapy, however local radiotherapy of isolated lesions with palliative intent is acceptable.

Follow-up	Approximately 40 months
Primary Outcomes	Overall survival (Time frame: up to 40 months)

Secondary Outcomes	• Progression-free survival (Time frame: up to 40 months) • Objective response (Time frame: up to 40 months) • Duration of response (Time frame: up to 40 months) • Disease control (Time frame: up to 40 months) • Cmax (Time frame: up to 40 months) • Ctrough (Time frame: up to 40 months) • Incidence of anti-drug antibody (Time frame: up to 40 months) • Tumour tissue biomarker (Time frame: up to 40 months) • Functional Assessment of Cancer Therapy –Bladder Cancer (Time frame: up to 40 months) • EuroQoL EQ-5D (Time frame: up to 40 months)
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Estimated primary completion date reported as June 2020. Estimated study completion date reported as June 2021.

ESTIMATED COST

Avelumab is already marketed in the UK; a 200mg/10ml (20 mg/1ml) concentrate for solution for infusion vial costs £768.00.[22]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance in development. Atezolizumab with gemcitabine and carboplatin for treating metastatic urothelial bladder cancer (GID-TA10202). Expected publication date to be confirmed.
- NICE technology appraisal guidance in development. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (GID-TA10466). Expected publication date 15 January 2020.
- NICE guideline. Bladder cancer: Diagnosis and management (NG2). February 2015

NHS ENGLAND (POLICY/COMMISSIONING) GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). N15/S/a.
- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. 16033/P. 2016

OTHER GUIDANCE

- European Association of Urology. Muscle-invasive and Metastatic Cancer. 2018.[23]
- European Society for Medical Oncology (ESMO). Bladder cancer: ESMO practice Guidelines for diagnosis, treatment and follow-up. 2014.[24]

ADDITIONAL INFORMATION

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