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HEALTH TECHNOLOGY BRIEFING
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Enfortumab vedotin for locally advanced or metastatic urothelial cancer

NIHRIO ID	13663	**NICE ID**	10381
Developer/Company	Astellas Pharma Ltd	**UKPS ID**	657953

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

SUMMARY

Enfortumab vedotin is currently in clinical development for the treatment of locally advanced or metastatic urothelial cancer in patients who have previously received chemotherapy and immunotherapy. Urothelial cancer, a subset of bladder cancer, occurs on the lining of the renal pelvis, ureter, bladder and urethra, and other parts of the urinary system. In advanced urothelial cancer, the cancer has grown 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. There are currently limited treatment options for patients with advanced or metastatic urothelial cancer that have progressed after treatment with chemotherapy or immunotherapy.

Enfortumab vedotin is an antibody-drug conjugate that is administered intravenously. It works by selectively targeting the protein Nectin-4 which is found in high quantities in the cells of bladder cancer patients. When Enfortumab vedotin attaches to Nectin-4 it causes the release of an anticancer agent, resulting in cancer cell death. Enfortumab vedotin has been demonstrated to be safe and efficacious in earlier clinical studies. If licensed, it may provide a treatment option for patients with advanced or metastatic urothelial cancer whose disease has progressed after being previously treated with chemotherapy and immunotherapy.

PROPOSED INDICATION

Adults with locally advanced or metastatic urothelial carcinoma who have previously been treated with chemotherapy and a checkpoint inhibitor (PD-1 or PD-L1).[1]

TECHNOLOGY

DESCRIPTION

Enfortumab vedotin (Padcev; ASG-22ME) is an antibody-drug conjugate which comprises a Nectin-4 directed human immunoglobulin G1 (IgG1) antibody and a microtubule-disrupting agent Monomethyl Auristatin E (MMAE). Nectin-4 is a cell surface protein highly expressed in bladder cancer patients. Enfortumab vedotin binds to the Nectin-4 expressing cells, resulting in the internalisation of the enfortumab vedotin-Nectin-4 complex and release of the toxin MMAE by proteolytic cleavage. The release of MMAE into the microtubule network within the cell causes cell cycle inhibition and cell death.[2]

Enfortumab vedotin is currently in clinical development for the treatment of patients with locally advanced or metastatic urothelial cancer who have previously been treated with an immune checkpoint inhibitor. In the phase III clinical trial EV-301 (NCT03474107, Eudra CT 2017-003344-21) patients are given enfortumab vedotin by intravenous infusion over 30 minutes on days 1, 8 and 15 of each 28 day cycle.[1,3]

INNOVATION AND/OR ADVANTAGES

Currently there are no approved therapies in the UK for locally advanced or metastatic urothelial cancer that work via the Nectin-4-directed antibody-drug conjugate mechanism.[4] Nectin-4 is overexpressed in urothelial cancer and the delivery of MMAE by Enfortumab vedotin has demonstrated significant clinical benefit.[5]

Results from the phase II trial EV-201 (NCT03219333) demonstrated that enfortumab vedotin is the first novel medicinal product to demonstrate substantial clinical activity in urothelial cancer patients who have progressed after platinum chemotherapy and a PD-1/L1 inhibitor.[3,5]

DEVELOPMENT STATUS AND/OR REGULATORY DESIGNATIONS

Enfortumab vedotin does not currently have Marketing Authorisation in the EU/UK for any indication.

Enfortumab vedotin was granted accelerated approval by the FDA for the treatment of metastatic urothelial cancer in the US in December 2019.[6]

Enfortumab vedotin is currently in phase II clinical development for metastatic malignant solid tumours and phase III clinical development as a combination therapy for metastatic urothelial cancer.[7]

PATIENT GROUP

DISEASE BACKGROUND

Urothelial cancer (also known as transitional cell carcinoma) is the most common type of bladder cancer, accounting for 90% of bladder cancer cases in the UK.[8] Urothelial cancer develops from the urothelial cells that line the urethra, bladder, ureters, renal pelvis and some other organs.[9] When the bladder is empty, these cells are all bunched together and as the bladder fills with urine the cells stretch out into a single layer. These cells come into contact with waste products in the urine that may cause cancer, such as chemicals from cigarette smoke.[8]

Cancer cells can break away from where they began (the primary tumour) and travel through the lymph system or blood. When cancer spreads to another part of the body it is referred to as metastatic cancer.[10] Locally advanced cancer describes cancer that has grown outside the organ it started but has not yet spread to distant parts of the body.[11] Cancer stage (referring to the extent of the cancer) can be described using the TNM staging system:[8]

- T (TX-T4) refers to the size and extent of the main tumour. The higher the number after T, the larger the tumour or the more it has grown into nearby tissues.
- N (NX-N4) refers to the number of nearby lymph nodes that have cancer. The higher the number after the N, the more lymph nodes that contain cancer.
- M (M0-M1) refers to whether the cancer has metastasized. M0 indicates no metastases.

The single biggest risk factor for urothelial cancer is smoking and it is estimated that more than a third of all cases are caused by smoking. Exposure to certain industrial chemicals such as aniline dyes, 2-Naphthylamine, 4-Aminobiphenyl, xenylamine, benzidine and o-toluidine is the second biggest risk factor. It is estimated they may account for around 25% of urothelial cancer cases. Other risk factors include: radiotherapy to treat previous cancers, previous treatment with some chemotherapy medications, having type 2 diabetes, long-term or repeated urinary tract infections, early menopause, and long-term bladder stones.[12]

Blood in the urine (haematuria) is the most common symptom of urothelial cancer. Less common symptoms include: more frequent need to urinate, sudden urges to urinate and a burning sensation when passing urine. If urothelial cancer reaches an advanced stage and begins to spread, symptoms can include: pelvic pain, bone pain, unintentional weight loss and swelling of the legs.[13]

CLINICAL NEED AND BURDEN OF DISEASE

Bladder cancer is the 11th most common cancer in the UK, accounting for 3% of all new cancer cases. Bladder cancer is more common in males than females, accounting for 73% of cases vs 27% respectively. In 2017, the incidence rate of bladder cancer in the UK was 8.4 cases per 100,000 in females and 23.0 cases per 100,000 in males.[14] Bladder cancer incidence is strongly related to age. Age-specific incidence rates rise gradually from around age 50-54 in both males and females, with a sharper rise in males from age 60-64. The highest rates are in the 90+ age group for females and males.[15] The European age-standardised incidence rate of bladder cancer in the UK is projected to decrease by 2035 to 21.07 per 100,000 (7,531 projected cases).[16]

In England, in 2017, there were 8,686 new registrations for malignant neoplasm of bladder (ICD-10 code C67), 692 for malignant neoplasm of renal pelvis (ICD-10 code C65) and 596

for malignant neoplasm of ureter (ICD-10 code C66). The direct age-standardised rates per 100,000 population were 27.6 among males and 8.2 among females for malignant neoplasm of bladder. The direct age standardised rates were low for malignant neoplasm of renal pelvis (1.8 for males and 1.0 for females) and malignant neoplasm of ureter (1.7 for males and 0.7 for females).[17]

In 2018-19, there were 73,789 finished consultant episodes (FCE) in England for malignant neoplasm of bladder resulting in 69,198 admissions and 100,777 FCE bed days. There were 1,533 FCEs for malignant neoplasm of renal pelvis (1,386 admissions and 3,219 bed days); and 2,445 FCEs for malignant neoplasm of ureter (2,157 admissions and 5,579 bed days).[18]

In 2017, there were 5,014 deaths (3,441 male and 1,573 female) in England and Wales recorded with malignant neoplasm of bladder as the cause (ICD-10 code C67).[19] The one year net cancer survival for stage IV bladder cancer in adults was 35.7% with no data recorded for five year net cancer survival. (2013-2017).[20] The European age-standardised mortality rate in the UK is projected to decrease by 2035 to 9.39 per 100,000 (7,771 projected deaths) for bladder cancer.[21]

PATIENT TREATMENT PATHWAY

TREATMENT PATHWAY

The aim of treatment for advanced urothelial cancer is to slow down cancer progression and reduce any symptoms.[22] A specialist urology multidisciplinary team (comprising of urologists, pathologists, radiologists and a specialist clinical nurse) is normally employed throughout the treatment. Treatment options for advanced or metastatic urothelial cancer depends on how far the cancer has spread. The options include: chemotherapy, immunotherapy and treatments to relieve cancer symptoms. If the cancer is too advanced, palliative care may be offered to manage pain.[23]

CURRENT TREATMENT OPTIONS

In the current NICE pathway for managing locally advanced metastatic bladder cancer there are no recommended therapies in patients that have progressed after second-line treatment with chemotherapy and PD-1/L1 inhibitors.[24]

PLACE OF TECHNOLOGY

If licensed, enfortumab vedotin will offer a treatment option for adult patients with locally advanced or metastatic urothelial cancer who have been previously treated with platinum chemotherapy and PD-1/PD-L1.

CLINICAL TRIAL INFORMATION

Trial	**EV-301,** NCT03474107, EudraCT 2017-003344-21; An Open-Label, Randomized Phase 3 Study to Evaluate Enfortumab Vedotin vs Chemotherapy in Subjects With

	Previously Treated Locally Advanced or Metastatic Urothelial Cancer (EV-301) **Phase III -** Active, not recruiting **Locations**: EU countries (incl UK), USA, Canada and other countries **Estimated Primary Completion Date:** September 2021
Trial design	Randomized, Parallel Assignment, Open-label
Population	N=608; adults aged 18 years and older; subjects with histologically or cytologically confirmed urothelial carcinoma; radiographic progression or relapse during or after a checkpoint inhibitor for locally advanced or metastatic disease; must have received a platinum containing regimen (cisplatin or carboplatin) in the metastatic/locally advanced, neoadjuvant or adjuvant setting, If platinum was administered in the adjuvant/neoadjuvant setting subject must have progressed within 12 months of completion; radiologically documented metastatic or locally advanced disease at baseline
Intervention(s)	Enfortumab vedotin (intravenous administration) Given on days 1, 8 and 15 of each 28 day cycle
Comparator(s)	Chemotherapy given on day 1 of each 21 day cycle. One of: - docetaxel (intravenous administration) - vinflunine (intravenous administration) - paclitaxel (intravenous infusion)
Outcome(s)	Overall Survival [Time Frame: Up to 36 months] See trial record for full list of outcomes
Results (efficacy)	-
Results (safety)	-

Trial	**EV-201,** NCT03219333, EudraCT 2017-003479-78; A Single-arm, Open-label, Multicenter Study of Enfortumab Vedotin (ASG-22CE) for Treatment of Patients With Locally Advanced or Metastatic Urothelial Cancer Who Previously Received Immune Checkpoint Inhibitor (CPI) Therapy **Phase II - Active, not recruiting** **Locations:** EU countries (not incl UK), USA and other countries **Estimated Primary Completion Date:** November 2020
Trial design	Single-arm, Open-label, multi-cohort, multicentre
Population	N=219; adults aged 18 years and older; histologically documented urothelial carcinoma; metastatic disease or locally advanced disease that is not resectable; received prior treatment with a check point inhibitor in the locally advanced or metastatic urothelial cancer setting; received prior treatment with platinum-containing chemotherapy or be platinum-naïve and ineligible for treatment with cisplatin at time of enrolment; progression or recurrence of urothelial cancer during or following receipt of most recent therapy.
Intervention(s)	1.25mg/kg enfortumab vedotin on days 1, 8 and 15 every 28 days (intravenous infusion).[25]
Comparator(s)	No comparator

Outcome(s)	Objective response rate [Time Frame: Up to 3 years] See trial record for full list of outcomes
Results (efficacy)	Confirmed objective response rate was 44%, including 12% complete responses. Median duration of response was 7.6 months.[25]
Results (safety)	The most common treatment-related adverse events (TRAEs) were fatigue (50%), any peripheral neuropathy (50%), alopecia (49%), any rash (48%), decreased appetite (44%) and dysgeusia (40%). The most common grade 3 or greater TRAEs were neutropenia (8%), anaemia (7%) and fatigue (6%). Febrile neutropenia (4%) was the most common serious TRAE. TRAEs led to dose reductions in 32% of patients and discontinuation in 12% of patients. Peripheral sensory neuropathy was the most common TRAE that led to dose reduction (9%) and discontinuation (6%).[25]

ESTIMATED COST

The estimated cost of enfortumab vedotin is not yet known.

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE technology appraisal guidance. Nivolumab for treating locally advanced unresectable or metastatic urothelial cancer after platinum-containing chemotherapy (TA530). July 2018.
- NICE technology appraisal guidance. Atezolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA525). June 2018.
- NICE technology appraisal guidance. Pembrolizumab for treating locally advanced or metastatic urothelial carcinoma after platinum-containing chemotherapy (TA519). April 2018.
- NICE technology appraisal guidance. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272). January 2013.
- NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS106). 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 Cancer. 2020.[26]
- European Society of Medical Oncology (ESMO). ESMO bladder cancer practice guidelines for diagnosis, treatment and follow-up. 2014.[27]

ADDITIONAL INFORMATION

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