Health Technology Briefing
November 2022

Enfortumab vedotin with pembrolizumab for previously untreated locally advanced or metastatic urothelial cancer

Company/Developer	Astellas Pharma Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 29564	NICE TSID: 10556	UKPS ID: 666945

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Enfortumab vedotin in combination with pembrolizumab is in clinical development for the treatment of patients with previously untreated locally advanced or metastatic urothelial cancer (UC). UC occurs on the lining of the renal pelvis, ureter, bladder and urethra, and other parts of the urinary system. Metastatic UC occurs when the cancer has spread to other parts of the body. Durable responses are rare with current standard of care treatments. Therefore, treatment approaches with longer-term disease control and extending to broader metastatic UC patient populations are needed.

Enfortumab vedotin is an antibody (a type of protein) combined with another substance known as MMAE. It works by selectively targeting the protein Nectin-4 which is found in high quantities in the cells of urothelial cancer. When enfortumab vedotin attaches to Nectin-4, it causes the release of an anticancer agent (MMAE), resulting in cancer cell death. Pembrolizumab is a monoclonal antibody, a protein that has been designed to recognise and block a target (receptor) called PD-1. By blocking PD-1, pembrolizumab stops the cancer switching off immune cells, thereby increasing the immune system's ability to kill the cancer cells. Both enfortumab vedotin and pembrolizumab are administered intravenously. If licensed, enfortumab vedotin in combination with pembrolizumab would provide a treatment option for patients with untreated locally advanced or metastatic urothelial cancer.

Proposed Indication

For the treatment of patients with previously untreated locally advanced or metastatic urothelial cancer (UC).[1]

Technology

Description

Enfortumab vedotin (ASG-22ME, Padcev) is an antibody drug conjugate (ADC) containing a human monoclonal antibody AGS-22 targeting the cell adhesion molecule nectin-4 and conjugated to the cytotoxic agent monomethyl auristatin E (MMAE), via a proprietary enzyme-cleavable linker (AGS22CE), with potential antineoplastic activity.[2] The monoclonal antibody moiety of AGS-22CE selectively binds to nectin-4. After internalization and proteolytic cleavage, MMAE binds to tubulin and inhibits its polymerization, which results in G2/M phase arrest and induces apoptosis in nectin-4 overexpressing tumour cells. Nectin-4, a tumour associated antigen belonging to the nectin family, is overexpressed in a variety of cancers, including breast, bladder, lung and pancreatic cancer.[2]

Pembrolizumab (Keytruda) is a humanised monoclonal antibody which binds to the programmed cell death-1 (PD-1) receptor and blocks its interaction with 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. Pembrolizumab potentiates T-cell responses, including anti-tumour responses, through blockade of PD-1 binding to 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.[3]

Enfortumab vedotin in combination with pembrolizumab is in clinical development for the treatment of patients with previously untreated locally advanced or metastatic UC. In the phase III clinical trial (EV-302; NCT04223856), enfortumab vedotin is administered by intravenous (IV) infusion on day 1 and day 8 of every 3-week cycle in combination with pembrolizumab administered by IV infusion on day 1 of each 3-week cycle.[1]

Key Innovation

Currently, the standard first line treatment for patients with untreated, cisplatin-eligible unresectable or metastatic UC is cisplatin-based chemotherapy.[4] Regimens containing cisplatin have been the standard of care for metastatic UC for nearly 40 years, but durable response is rare with such treatment regimens. Furthermore, a large proportion of patients with unresectable or metastatic UC are ineligible for cisplatin-based chemotherapy. There is a need for treatment approaches conferring longer-term disease control that extend to patients with metastatic UC.[5]

Enfortumab vedotin is a novel, potentially first-in-class ADC.[6] Enfortumab vedotin has previously shown an overall survival benefit versus chemotherapy in patients with locally advanced or metastatic UC who had previously received platinum-based therapy and a PD-(L)1 inhibitor. Preclinical studies showed that MMAE containing ADCs, including enfortumab vedotin, induce evidence of immunogenic cell death and can enhance anti-tumour immunity, thereby laying the foundation for enfortumab vedotin-PD-1/PD-L1 inhibitor combination.[7]

If licensed, enfortumab vedotin in combination with pembrolizumab would provide an alternative first-line treatment option for patients with locally advanced or metastatic UC.

Regulatory & Development Status

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

Enfortumab vedotin as monotherapy has Marketing Authorisation in the EU/UK for the treatment of adult patients with locally advanced or metastatic UC who have previously received a platinum-containing chemotherapy and a programmed death receptor-1 or programmed death-ligand 1 inhibitor.[8]

Pembrolizumab as monotherapy and in combination has Marketing Authorisation in the EU/UK for the following indications:[3]

- non-small cell lung cancer (NSCLC)
- classical Hodgkin lymphoma
- melanoma
- UC
- head and neck squamous cell carcinoma (HNSCC)
- renal cell carcinoma
- oesophageal cancer
- triple-negative breast cancer
- endometrial carcinoma
- Microsatellite instability high (MSI-H) or mismatch repair deficient (dMMR) cancers (colorectal and non-colorectal cancers)
- cervical cancer

Enfortumab vedotin in combination with pembrolizumab is currently in phase III clinical trial for muscle invasive bladder cancer.[9]

Patient Group

Disease Area and Clinical Need

Urothelial cancer (UC), also called transitional cell carcinoma (TCC), is cancer that begins in the transitional cells that line the renal pelvis, ureters, bladder and urethra, and some other organs. These cells can change shape and stretch without breaking apart.[10] Metastatic UC occurs when the cancer has grown from where it started and has spread to other parts of the body, such as the liver or bones.[11] The main risk factors for bladder cancer include: smoking, bladder infections, medical conditions such as systemic sclerosis, as well as prior bladder cancer and family history, being overweight, and exposure to certain chemicals.[12] The symptoms of bladder cancer include blood in the urine, increased frequency/urgency of passing urine, pain or a burning sensation when passing urine, weight loss, back, lower abdomen or bone pain, fatigue and illness.[9]

UC is the most common type of bladder cancer.[13] UC accounts for about 90% of ureter or renal pelvis cancers.[14] 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).[15] In England in 2021-2022, there were 68,614 finished consultant episodes (FCE) for malignant neoplasm of bladder, resulting in 64,548 hospital admissions, 88,955 FCE bed days and 40,978 day cases. There were 1,696 FCE for malignant neoplasm of renal pelvis, resulting in

1,571 hospital admissions, 2,679 FCE bed days and 978 day cases. The FCE for malignant neoplasm of ureter were 2,625, resulting in 2,432 hospital admissions, 4,616 FCE bed days and 1,455 day cases.[16]

Recommended Treatment Options

For locally advanced or metastatic bladder cancer, treatment options may include chemotherapy, immunotherapy or treatment to relieve cancer symptoms.[17]

The first-line treatment options recommended by NICE for locally advanced or metastatic UC in adults include:[4,18]

- a cisplatin-based chemotherapy regimen
- carboplatin in combination with gemcitabine if a cisplatin-based chemotherapy regimen is unsuitable
- atezolizumab when cisplatin-containing chemotherapy is unsuitable

Clinical Trial Information

Trial	**EV-302;** NCT04223856; EudraCT 2019-004542-15; An Open-label, Randomized, Controlled Phase 3 Study of Enfortumab Vedotin in Combination With Pembrolizumab Versus Chemotherapy Alone in Previously Untreated Locally Advanced or Metastatic Urothelial Cancer **Phase III** - Recruiting **Location(s)**: 10 EU countries, UK, USA, Canada, and other countries **Primary completion date**: November 2023
Trial Design	Randomised, parallel assignment, open label
Population	N= 990 (estimated); 18 years and older; all sexes, Subjects with histologically documented, unresectable locally advanced or metastatic urothelial carcinoma
Intervention(s)	Enfortumab vedotin (IV) on days 1 and 8 of every 3 weeks cycle, plus pembrolizumab (IV) on day 1 of every 3-week cycle
Comparator(s)	Gemcitabine (IV) on days 1 and 8 of every 3 weeks cycle, plus cisplatin (IV) on day 1 of each 3-week cycle, plus carboplatin (IV) on day 1 of each 3-week cycle
Outcome(s)	• Duration of progression-free survival (PFS) per Response Evaluation Criteria in Solid Tumours (RECIST) v1.1 by blinded independent central review (BICR) (Arms A and B only) [Time Frame: Up to approximately 5 years] • Duration of Overall survival (OS) (Arms A and B only) [Time Frame: Up to approximately 5 years] See trial record for full list of other outcomes
Results (efficacy)	Most patients experienced tumour shrinkage. The median duration of response (DOR) and median overall survival (OS) exceeds 2 years in a cisplatin-ineligible patient population.[19]
Results (safety)	Enfortumab vedotin plus pembrolizumab showed a manageable safety profile.[19]

Estimated Cost

Enfortumab vedotin is already marketed in the UK; a 20mg vial costs £578, and a 30mg vial costs £867.[20]

Pembrolizumab is already marketed in the UK; a 100mg/4ml vial costs £2,630.[21]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Erdafitinib for treating metastatic or unresectable FGFR-positive urothelial cancer (GID-TA10252). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Durvalumab with tremelimumab and chemotherapy for treating unresectable or advanced urothelial cancer (GID-TA10748). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab with chemotherapy for untreated unresectable or metastatic urothelial cancer (GID-TA11010). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated PD-L1 positive unresectable or metastatic urothelial cancer (GID-TA10707). Expected date of issue to be confirmed.
- NICE technology appraisal in development. Nivolumab with ipilimumab for untreated unresectable or metastatic urothelial cancer when cisplatin is unsuitable (GID-TA10826). Expected date of issue to be confirmed.
- NICE Technology appraisal. Atezolizumab for untreated PD-L1-positive advanced urothelial cancer when cisplatin is unsuitable (TA739). October 2021.
- NICE technology appraisal guidance. Vinflunine for the treatment of advanced or metastatic transitional cell carcinoma of the urothelial tract (TA272). Jan 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

- Powles T, Bellmunt J, Comperat E, et al. Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. 2022.[22]
- European Association of Urology. Guidelines on muscle-invasive and metastatic bladder cancer. 2020.[23]

Additional Information

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