Health Technology Briefing
March 2023

Enfortumab vedotin with pembrolizumab for treating bladder cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ **New Active Substance** ☒ **Significant Licence Extension (SLE)**

NIHRIO ID:31114	**NICE ID:** 10718	**UKPS ID:** 666946

Licensing and Market Availability Plans

Currently in phase II and III clinical development.

Summary

Enfortumab vedotin in combination with pembrolizumab is in clinical development as a neoadjuvant treatment option for cisplatin eligible patients with non-metastatic muscle invasive bladder cancer (MIBC). MIBC is a cancer that spreads into the muscle layer of the bladder wall. The survival rates for patients with MIBC are low because this type of cancer is more likely to spread to other parts of the body. There is therefore a need to develop additional treatment options to improve prognosis outcomes.

The active substance in Padcev is enfortumab vedotin, consists of an antibody (a type of protein) combined with another substance known as microtubule-disrupting agent (MMAE). The antibody first attaches to a protein on the surface of the cancer cells to gain entry into the cells. Once the active substance is inside the cells, MMAE disrupts the cells' internal skeleton, causing cell death and helping to stop the cancer from getting worse or spreading.

Pembrolizumab is a monoclonal antibody, that has been designed to recognise and block a receptor ('target') called PD-1. By blocking the action of PD-L1, pembrolizumab stops the cancer switching off certain immune cells, thereby increasing the immune system's ability to kill the cancerous cells. Both enfortumab vedotin and pembrolizumab are administered intravenously. If licensed, enfortumab vedotin in combination with pembrolizumab would provide an additional neoadjuvant treatment option for cisplatin-eligible patients with non-metastatic MIBC.

Proposed Indication

Perioperative enfortumab vedotin with pembrolizumab for the treatment of cisplatin-eligible patients with muscle invasive bladder cancer (MIBC).[1]

Technology

Description

Enfortumab vedotin (Padcev) is an antibody drug conjugate (ADC) targeting Nectin-4, an adhesion protein located on the surface of the urothelial cancer cells. It is comprised of a fully human IgG1-kappa antibody conjugated to the microtubule-disrupting agent (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker. Nonclinical data suggest that the anticancer activity of enfortumab vedotin is due to the binding of the ADC to Nectin-4-expressing cells, followed by internalisation of the ADC-Nectin-4 complex, and the release of MMAE via proteolytic cleavage. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death. MMAE released from enfortumab vedotin targeted cells can diffuse into nearby Nectin-4 low-expressing cells resulting in cytotoxic cell death.[2,3]

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.[4]

Enfortumab vedotin in combination pembrolizumab is in clinical development for the neoadjuvant treatment of cisplatin-eligible patients with MIBC.[1,5] In the phase III clinical trial (NCT04700124), 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

More than 50% of patients with MIBC will experience a relapse and die from distant metastases despite local management with surgery or radiation. There is a need to develop more effective treatment options in the neoadjuvant setting to reduce the risk of relapse and improve the prognosis for MIBC.[6] Administering neoadjuvant therapy is highly beneficial in patients MIBC, as it increases the probability of downstaging the disease and indirectly associated with overall survival.[7-9]

Enfortumab vedotin and pembrolizumab are antibody drug conjugates, called monoclonal antibodies. This novel class of therapeutic compounds has been the subject of numerous studies because it has the potential to deliver chemotherapeutic medications to a particular target with increased therapeutic effectiveness and reduced toxicity.[10] Enfortumab vedotin in combination with pembrolizumab is a first line platinum-free regimen that showed promising antitumor activity and a manageable safety.[11] This combination has shown a survival benefit versus chemotherapy in urothelial cancer.[12] If licensed, enfortumab vedotin in combination with pembrolizumab would provide an alternative for MIBC patients perioperative, with a manageable safety profile.[1]

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 currently has Marketing Authorisation in the EU/UK, for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a programmed death receptor 1 or programmed death ligand 1 inhibitor.[2,3]

Pembrolizumab as a monotherapy currently has Marketing Authorisation in the EU/UK for several indications, including:[4]

- Melanoma
- Non-small-cell lung carcinoma
- Classical Hodgkin lymphoma
- Metastatic urothelial carcinoma
- Renal cell carcinoma
- Urothelial carcinoma

Enfortumab vedotin in combination with pembrolizumab is also in phase 2 and 3 clinical development for:[13]

- Untreated and treated locally advanced or metastatic urothelial cancer.
- High-risk upper tract urothelial cancer
- High grade upper tract urothelial cancer
- Locally advanced or metastatic bladder cancer of variant histology

Patient Group

Disease Area and Clinical Need

Bladder cancer is where a growth of abnormal tissue, known as a tumour, develops in the bladder lining. In some cases, the tumour spreads into the bladder muscle. If the cancerous cells are contained inside the lining of the bladder, it is described as non-muscle-invasive bladder cancer (early bladder cancer). This is the most common type of bladder cancer. When the cancerous cells spread beyond the lining, into the surrounding bladder muscle, it's referred to as muscle-invasive bladder cancer (or invasive bladder cancer), which is less common.[14] The most common symptom of bladder cancer is blood in urine, which is usually painless. Less common symptoms include; a need to urinate on a more frequent basis, sudden urges to urinate and a burning sensation when passing urine.[14] Risk factors include; tobacco smoking, exposure to harmful chemicals, infections, having a indwelling catheter for a long time, diabetes, long term bladder stones, and previous treatment with certain chemotherapy or radiotherapy.[15]

Bladder cancer is the 11th most common cancer in the UK, accounting for 3% of all new cancer cases.[16] Incidence rates for bladder cancer in the UK are highest in people aged 85 to 89 (2016-2018).[16] The age standardised incidence rate of bladder cancer in England is 6,323 and 2,351 per 100,000 amongst males and females respectively.[17] In England in 2021-2022, there were 68,614 finished consultant episodes (FCE) for malignant neoplasm of bladder (ICD-10 code C67), resulting in 64,548 hospital admissions, 88,955 FCE bed days and 40,978 day cases.[18,19] In England (2017), there were 8,686 patients diagnosed with malignant neoplasm of bladder and 5,600 deaths registered where bladder cancer was the underlying cause. For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 74.1% and 52.6% respectively.[16]

Recommended Treatment Options

The current treatment options recommended by NICE for adults with MIBC are:[20,21]

- Neoadjuvant chemotherapy for newly diagnosed MIBC using cisplatin combination regimen
- Radical cystectomy
- Radical radiotherapy
- Adjuvant chemotherapy after radical cystectomy

Clinical Trial Information	
Trial	**KEYNOTE-B15;** NCT04700124; 2020-003106-31; A phase 3, randomized, open-label study to evaluate perioperative enfortumab vedotin plus pembrolizumab (MK-3475) versus neoadjuvant gemcitabine and cisplatin in cisplatin-eligible participants with muscle-invasive bladder cancer **Phase III:** Recruiting **Location(s);** 11 EU countries, USA, Canada and other countries **Primary completion date:** December 2026
Trial Design	A parallel assigned, randomised, open label intervention trial
Population	N=784; 18 years and older; histologically confirmed diagnosis of urothelial carcinoma / muscle invasive bladder cancer, without metastasis; eligible for radical cystectomy + pelvic lymph node dissection
Intervention(s)	Participants receive 4 cycles (each cycle length = 21 days) of EV intravenous (IV) infusion plus pembrolizumab IV infusion preoperatively, followed by RC + PLND, followed by 5 cycles of adjuvant EV IV infusion plus 13 cycles of adjuvant pembrolizumab IV infusion postoperatively. The total treatment duration is up to approximately 1 year.
Comparator(s)	Neoadjuvant chemotherapy (gemcitabine + cisplatin) and RC + PLND Participants receive 4 cycles (each cycle length = 21 days) of standard of care (SOC) chemotherapy (gemcitabine IV infusion plus cisplatin IV infusion) preoperatively, followed by RC + PLND. The total treatment duration is up to approximately 3 months.
Outcome(s)	Primary outcome measure: • Event-Free Survival (EFS) [Time frame: up to ~68 months] See trial records for full list of other outcomes.
Results (efficacy)	
Results (safety)	

Trial	**EV-ECLIPSE;** NCT05239624; Enfortumab Vedotin in Combination with Pembrolizumab for Locally Advanced and/or Node Positive Urothelial Carcinoma Prior to Surgery **Phase II -** Recruiting **Location(s):** USA. **Primary Completion Date:** June 2024

Trial Design	A single group interventional open label trial design
Population	N=23; 18 years and older; adults and older adults, with histologically confirmed diagnosis of muscle invasive bladder cancer (previously known as transitional cell) carcinoma (i.e., cancer of the bladder, renal pelvis, ureter, or urethra); participants with no prior treatments for muscle invasive or metastatic urothelial carcinoma.
Intervention(s)	Enfortumab vedotin will be administered at 1.25 mg/kg on day 1 and day 8 of each 21-day cycle, for up to 6 cycles. Pembrolizumab will be administered on day 1 of each cycle, every 21 days, for 6 cycles. At completion of cycle 6, patients will have repeat imaging assessment and proceed to cystectomy within 4-8 weeks. Following cystectomy, patients will resume pembrolizumab monotherapy on day 1 of each 21-day cycle for an additional 11 doses (cycles 7-17), to complete 1 year of pembrolizumab therapy.
Comparator(s)	None
Outcome(s)	• Pathologic complete response rate [Time Frame: 2years] • Event-Free Survival [Time Frame: 2years]
Results (efficacy)	-
Results (safety)	-

Estimated Cost
Enfortumab vedotin is already marketed in the UK; a vial of 20mg costs £578, and a 30mg vial is £867.[22] Pembrolizumab is already marketed in the UK; a 100mg vial costs £2,630 (excluding VAT; company submission)[23]

Relevant Guidance
NICE Guidance
• NICE technology appraisal in development. Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of cisplatin-eligible muscle-invasive bladder cancer **(**GID-TA11122) Expected date of issue to be confirmed. • NICE technology appraisal in development. Durvalumab for neoadjuvant and adjuvant treatment of muscle-invasive bladder cancer (GID-TA11115) Expected date of issue to be confirmed. • NICE guideline. Bladder cancer: diagnosis and management (NG2). February 2015. • NICE Quality Standard. Bladder cancer (QS106). December 2015. • Improving outcomes in urological cancers. Cancer service guideline (CSG2)**.** September 2002**.**
• 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 et al. Bladder Cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow up. 2022.[24]
- European Association of Urology. Guidelines on muscle-evasive and metastatic bladder cancer. 2022.[6]

Additional Information

References

1 ClinicalTrials.gov. *A Phase 3, Randomized, Open-label Study to Evaluate Perioperative Enfortumab Vedotin Plus Pembrolizumab (MK-3475) Versus Neoadjuvant Gemcitabine and Cisplatin in Cisplatin-eligible Participants With Muscle-invasive Bladder Cancer (KEYNOTE-B15 / EV-304)*. *Trial ID: NCT04700124*. 2021. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT04700124?id=NCT04700124+OR+NCT05239624&draw=2&rank=2&load=cart [Accessed 30 January 2023].

2 Electronic Medicines Compedium. *Padcev 20 mg powder for concentrate for solution for infusion*. 2022. Available from: https://www.medicines.org.uk/emc/product/13669/smpc [Accessed 30 January 2023].

3 European Medicines Agency. *Padcef- Enfortumab Vedotin*. 2022. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/padcev [Accessed 30 January 2023].

4 Electronic Medicines Compedium. *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. Available from: https://www.medicines.org.uk/emc/product/2498 [Accessed 20 February 2023].

5 ClinicalTrials.gov *Enfortumab Vedotin in Combination With Pembrolizumab for Locally Advanced and/or Node Positive Urothelial Carcinoma Prior to Surgery (EV-ECLIPSE)*. *Trial ID: NCT05239624*. 2022. Status: Recruiting. Available from: https://clinicaltrials.gov/ct2/show/NCT05239624?id=NCT04700124+OR+NCT05239624&draw=2&rank=1&load=cart [Accessed 30 January 2023].

6 European Association of Urologists (EAU). *Guidelines-Muscle-invasive and Metastatic Bladder Cancer*. 2022. Available from: https://uroweb.org/guidelines/muscle-invasive-and-metastatic-bladder-cancer [Accessed 31 January 2023].

7 Møller CT, Støer NC, Blindheim A, Berge V, Tafjord G, Fosså SD, et al. Downstaging and survival after Neoadjuvant chemotherapy for bladder cancer in Norway; a population-based study. *BMC Cancer*. 2022;22(1):1301. Available from: https://doi.org/10.1186/s12885-022-10394-w.

8 Yin M, Joshi M, Meijer RP, Glantz M, Holder S, Harvey HA, et al. Neoadjuvant Chemotherapy for Muscle-Invasive Bladder Cancer: A Systematic Review and Two-Step Meta-Analysis. *Oncologist*. 2016;21(6):708-15. Available from: https://doi.org/10.1634/theoncologist.2015-0440.

9 Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. *Eur Urol*. 2005;48(2):202-5; discussion 5-6. Available from: https://doi.org/10.1016/j.eururo.2005.04.006.

10 Alley SC, Okeley NM, Senter PD. Antibody–drug conjugates: targeted drug delivery for cancer. *Current Opinion in Chemical Biology*. 2010;14(4):529-37. https://www.sciencedirect.com/science/article/pii/S136759311000075X.
11 Hoimes CJ, Flaig TW, Milowsky MI, Friedlander TW, Bilen MA, Gupta S, et al. Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer. *Journal of Clinical Oncology*. 2023;41(1):22-31. Available from: https://doi.org/10.1200/jco.22.01643.
12 Hoimes CJ, Flaig TW, Milowsky MI, Friedlander TW, Bilen MA, Gupta S, et al. Enfortumab Vedotin Plus Pembrolizumab in Previously Untreated Advanced Urothelial Cancer. *J Clin Oncol*. 2023;41(1):22-31. Available from: https://doi.org/10.1200/jco.22.01643.
13 ClinicalTrials.gov. *Search of Enfortumab plus pembrolizumab, Recruiting, Not yet recruiting, Active, not recruiting,*. 2022-2023. Status: Phase 2,3. Available from: https://clinicaltrials.gov/ct2/results?term=Enfortumab+vedotin+and+pembrolizumab&draw=2&rank=3#rowId2 [Accessed 20 February 2023].
14 National Health Services (NHS). *Bladder Cancer-Symptoms*. 2021. Available from: https://www.nhs.uk/conditions/bladder-cancer/symptoms/.
15 Cancer Research UK. *Risks and causes of bladder cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/risks-causes [Accessed 30 January 2023].
16 Cancer Research UK. *Bladder Cancer Statistics*. 2015. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer#heading-Zero [Accessed 30 January 2023].
17 Cancer Research UK. *Bladder cancer incidence statistics*. 2021. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer/incidence#heading-Zero [Accessed 20 February 2023].
18 Office for National Statistics. *Cancer Registration Statistics: England 2017*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/2017 [Accessed 30 January 2023].
19 NHS Digital. *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22 [Accessed 31 January 2023].
20 National Health Service (NHS). *Treatment-Bladder Cancer*. 2021. Available from: https://www.nhs.uk/conditions/bladder-cancer/treatment/ [Accessed 30 January 2023].
21 National Institute of Health and Care Excellence (NICE). *Bladder Cancer: diagnosis and management. NICE guideline [NG2]*. 2015. Available from: https://www.nice.org.uk/guidance/ng2 [Accessed 30 January 2023].
22 British National Formulary (BNF). *Enfortumab Vedotin- Medicinal Forms*. Available from: https://bnf.nice.org.uk/drugs/enfortumab-vedotin/medicinal-forms/ [Accessed 31 January 2023].
23 British National Formulary (BNF). *Pembrolizumab-Medicinal Forms*. Available from: https://bnf.nice.org.uk/drugs/pembrolizumab/medicinal-forms/ [Accessed 31 January 2023].
24 Powles T, Bellmunt J, Comperat E, De Santis M, Huddart R, Loriot Y, et al. Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology*. 2022;33(3):244-58. Available from: https://doi.org/https://doi.org/10.1016/j.annonc.2021.11.012.

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.