Health Technology Briefing
November 2024

Enfortumab vedotin with pembrolizumab as perioperative therapy for previously untreated cisplatin-ineligible, muscle-invasive bladder cancer

Company/Developer	Astellas Pharma Ltd and MSD

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

NIHRIO ID: 27173	**NICE ID:** 10716	**UKPS ID:** 668545, 659331

Licensing and Market Availability Plans

Currently in phase III clinical development

Summary

Enfortumab vedotin in combination with pembrolizumab is currently in clinical development as a perioperative (around the time of surgery) treatment for patients with untreated muscle-invasive bladder cancer (MIBC), who are ineligible or refuse cisplatin therapy (a type of chemotherapy). 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. The current treatment option for MIBC patients includes chemotherapy given prior to main treatment, e.g., surgery (neoadjuvant). The chemotherapy drug given to treat MIBC is called cisplatin. However, some patients are unable to receive this type of chemotherapy, which increases their risk of cancer spreading to other parts of the body. There is therefore a need to develop additional treatment options to improve prognosis outcomes.

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 then enter the cells. Once the active substance is inside the cells, MMAE disrupts the cells' internal structure, causing cell death and helping to stop the cancer from developing. Pembrolizumab is a type of targeted therapy drug called an immune checkpoint inhibitor (a type of immunotherapy). It is a monoclonal antibody that binds to the protein PD-1 on the surface of immune cells called T cells. It works by keeping cancer cells from suppressing the immune system. This allows the immune system to attack and kill the cancer cells. If licensed, enfortumab vedotin in combination with pembrolizumab would provide an additional first-line perioperative treatment option for cisplatin-eligible patients with non-metastatic MIBC.

This briefing reflects the evidence available at the time of writing and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information. A version of the briefing was sent to the company for a factual accuracy check. The company was available to comment.

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Proposed Indication

Perioperative treatment for patients with non-metastatic muscle-invasive bladder cancer (MIBC) who are cisplatin-ineligible or decline cisplatin.[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]

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 perioperative treatment of patients with MIBC who are ineligible for (or decline) treatment with cisplatin. In the phase III clinical trial (NCT03924895), 1.25 mg/kg enfortumab vedotin will be administered by intravenous (IV) infusion, given on days 1 and 8 of each 21-day cycle in combination with 200mg pembrolizumab administered by IV infusion, given on day 1 of each 21-day cycle. Patients from the experimental and active comparator arms will receive radical cystectomy and pelvic lymph node dissection (standard of care surgery).[1]

Key Innovation

The current treatment paradigm for MIBC consists of cisplatin-based neoadjuvant chemotherapy followed by local definitive therapy.[4] However, an absolute threshold of creatinine clearance (CrCl) ≥60 ml/min excludes up to 50% of patients with MIBC from receiving cisplatin-based neoadjuvant chemotherapy.[4] Neoadjuvant chemotherapy followed by radical cystectomy is the standard treatment for cisplatin-eligible patients with MIBC cancer. Adding perioperative immunotherapy may improve outcomes.[5]

ADCs and checkpoint inhibitors (immunotherapy) have complementary mechanisms of action that provide different therapeutic effects. Checkpoint inhibitors as a monotherapy enhance the immune system's ability to kill tumour cells, whilst ADCs as a monotherapy directly target and eliminate tumour cells. The combined use of ADCs and checkpoint inhibitors has a synergistic effect, which can enhance therapeutic effects of each.[6] Enfortumab vedotin and pembrolizumab have individually been associated with a survival benefit in patients with previously treated locally advanced or metastatic urothelial carcinoma.[7-11] Therefore, if licensed, perioperative enfortumab vedotin in combination with pembrolizumab may provide further treatment options for patients with MIBC who are not eligible for standard cisplatin therapy.

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Regulatory & Development Status

Enfortumab vedotin in combination with pembrolizumab currently has Marketing Authorisation in the EU/UK for adult patients with unresectable or metastatic urothelial cancer who are eligible for platinum-containing chemotherapy.[2]

Enfortumab vedotin currently has Marketing Authorisation in the EU/UK as monotherapy for the treatment of adult patients with locally advanced or metastatic urothelial cancer who have previously received a platinum-containing chemotherapy and a PD-1 receptor or PD-L1 inhibitor: [2]

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

- Non-small cell lung cancer (NSCLC)
- Head and neck cancer
- Renal cell carcinoma
- Carcinoma of oesophagus
- Breast cancer
- Endometrial carcinoma
- Cervical cancer
- Gastric cancer
- Biliary tract cancer

Pembrolizumab as a monotherapy currently has Marketing Authorisation in the EU/UK for several indications including:[3]

- Melanoma
- NSCLC
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Colorectal cancer
- Triple-negative breast cancer

Enfortumab vedotin in combination with pembrolizumab is also in phase III/II clinical development for renal pelvis and urothelial carcinoma and solid tumors.[12]

Patient Group

Disease Area and Clinical Need

Bladder cancer is when abnormal cells in the bladder lining start to grow and divide in an uncontrolled way.[13] The most common type of bladder cancer is urothelial bladder cancer (or transitional cell bladder cancer). Urothelial cancer develops from the cells of the bladder lining (urothelium), and can become invasive when it has grown into a deeper (muscle) layer of the bladder, or beyond. MIBC needs more intensive treatment than non-MIBC. This is because there is a risk that it could spread to other parts of the body.[14] Cisplatin-based chemotherapy constitutes the cornerstone of treatment in most bladder cancer settings, however, multiple factors affect the ability to safely receive cisplatin, including comorbidities such as renal insufficiency, grade ≥ 2 neuropathy or hearing loss and symptomatic heart failure, all of which may render patients cisplatin-ineligible.[15] Risk factors include smoking, exposure to

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chemicals at work, aromatic amines, polycyclic aromatic hydrocarbons, having a catheter in for a long time, having radiotherapy and the infection schistosomiasis (bilharzia).[16] Blood in the urine is the most common symptom of bladder cancer, other symptoms can include pain or a burning sensation when passing urine, weight loss for no reason, pain in the back, lower stomach or bones, and feeling tired and unwell.[17]

Bladder cancer is one of the ten most common cancers in the UK.[18] About 90 out of 100 bladder cancers in the UK are urothelial cancer, with the potential to develop into MIBC.[14] About one-third of people diagnosed with bladder cancer have MIBC, which means approximately over 7,666 people in the UK are diagnosed with MIBC every year.[19, 20, 19] In the UK study (2013-2019), a total of 23,373 patients were diagnosed with MIBC. Chemotherapy was used in 37.8%, radiotherapy in 40.8%, and radical surgery in 23.7%; of these, 43.8% had surgery alone, 50.0% also received chemotherapy, 2.6% also received radiotherapy, and 3.5% had all three treatments. Survival rates have remained broadly similar over time, at approximately 60% at 1 year and 24.1% at 5 years.[21]

In England (2023-24) there were 70,218 finished consultant episodes (FCEs) and 66,254 admissions for neoplasm of the bladder (ICD-10 code C67), resulting in 46,193 day cases and 87,342 FCE bed days.[22] In England (2017), there were 8,686 patients diagnosed with malignant neoplasm of bladder (ICD-10 code C67) and 4,736 deaths registered where this was the underlying cause.[20]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) recommends neoadjuvant chemotherapy using a cisplatin combination regimen before radical cystectomy or radical radiotherapy to people with newly diagnosed MIBC for whom cisplatin-based chemotherapy is suitable. Radical cystectomy or radiotherapy with a radiosensitiser may be offered to those whom radical therapy is suitable. If cisplatin-based chemotherapy regimen is unsuitable then an **off-label** use of carboplatin in combination with gemcitabine may be offered.[24] There are currently no published NICE guidelines specifically indicated for the treatment of MIBC for cisplatin-based therapy ineligibility.

Clinical Trial Information

Trial	**MK-3475-905/KEYNOTE-905/EV-303; NCT03924895; EudraCT 2018-003809-26**; A Randomized Phase 3 Study Evaluating Cystectomy With Perioperative Pembrolizumab and Cystectomy With Perioperative Enfortumab Vedotin and Pembrolizumab Versus Cystectomy Alone in Participants Who Are Cisplatin-Ineligible or Decline Cisplatin With Muscle-Invasive Bladder Cancer **Phase III** – Active, not recruiting **Location(s)**: Ten EU countries, UK, USA, Canada and other countries **Primary Completion Date**: May 2027
Trial Design	Randomised, parallel assignment, open-label
Population	N=595 (actual); subjects with urothelial carcinoma/MIBC with predominant (≥50%) urothelial histology. Eligible for radical cystectomy (RC) and pelvic lymph node dissection (PLND), and agreement to undergo curative intent standard RC and PLND (including prostatectomy if applicable). Ineligible for treatment with cisplatin
Intervention(s)	• **Experimental: Arm A:** Pembrolizumab 200mg by intravenous (IV) infusion, given on day 1 of each 21-day cycle with surgery – radical cystectomy (RC) plus pelvic lymph node dissection (PLND)

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	• **Experimental: Arm C:** Enfortumab vedotin 1.25mg/kg by IV infusion, given on days 1 and 8 of each 21-day cycle. Participants receive 3 preoperative cycles of enfortumab vedotin + pembrolizumab, followed by standard of care surgery (RC plus PLND), followed by 6 cycles of postoperative enfortumab vedotin + pembrolizumab, followed by 8 cycles of pembrolizumab alone
Comparator(s)	• **Active comparator: Arm B:** Surgery alone: RC plus PLND
Outcome(s)	Event-Free Survival (EFS) between Arm C and Arm B. EFS is defined as the time from randomisation to the first occurrence of any of the following events: progression of disease that precludes RC surgery or failure to undergo RC surgery in participants with residual disease, gross residual disease left behind at the time of surgery, local or distant recurrence as assessed by imaging and/or biopsy, or death due to any cause.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; one vial 100mg/4ml concentrate for solution for infusion vial costs £2,600 (NHS indicative price).[25]

Enfortumab vedotin is already marketed in the UK; one vial 20mg powder for concentrate for solution for infusion vial costs £578.00 (NHS indicative price).[26]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Durvalumab for neoadjuvant and adjuvant treatment of muscle-invasive bladder cancer (TA11115). Expected publication date to be confirmed.
- NICE technology appraisal in development. Nivolumab with BMS-986205 and chemotherapy for neoadjuvant treatment of muscle-invasive bladder cancer (TA11336). Expected publication date to be confirmed.
- NICE technology appraisal in development. Durvalumab with enfortumab vedotin for neoadjuvant and adjuvant treatment of muscle-invasive bladder cancer when cisplatin is unsuitable (TA11517). Expected publication date to be confirmed.
- NICE technology appraisal in development. Pembrolizumab adjuvant for urothelial carcinoma and/or localised muscle invasive bladder cancer (TA11556). Expected publication date to be confirmed.
- NICE clinical guidance. Bladder cancer: diagnosis and management (NG2). February 2015
- NICE quality standard. Bladder cancer (QS106). December 2015

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Chemotherapy (Adult). B15/S/a
- NHS England. 2013/14. NHS Standard Contract for Cancer: Specialised Kidney, Bladder and Prostate Cancer Services (Adult). B14/S/a

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- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a
- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. July 2016. 160333/P

Other Guidance

- European Society for Medical Oncology (ESMO). Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment, and follow-up. 2024.[27]
- European Society of Urology. Muscle-invasive and Metastatic Bladder Cancer. 2024.[28]

Additional Information

References

1 ClinicalTrials.gov. *A Randomized Phase 3 Study Evaluating Cystectomy With Perioperative Pembrolizumab and Cystectomy With Perioperative Enfortumab Vedotin and Pembrolizumab Versus Cystectomy Alone in Participants Who Are Cisplatin-Ineligible or Decline Cisplatin With Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303). Trial ID: NCT03924895*. Available from: https://clinicaltrials.gov/study/NCT03924895 [Accessed 25 October 2024].

2 Electronic Medicines Copendium (EMC). *Padcev 20 mg powder for concentrate for solution for infusion*. 2024. Available from: https://www.medicines.org.uk/emc/product/13669/smpc [Accessed 18 October 2024].

3 Electronic Medicines Copendium (EMC). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. 2024. Available from: https://www.medicines.org.uk/emc/product/2498/smpc [Accessed 18 October 2024].

4 Nature Reviews Urology. *Defining cisplatin eligibility in patients with muscle-invasive bladder cancer*. 2021. Available from: https://www.nature.com/articles/s41585-020-00404-6#:~:text=An%20absolute%20threshold%20of%20creatinine%20clearance%20%28CrCl%29%20%E2%89%A560%E2%80%89ml%2Fmin,chemotherapy%20and%20might%20be%20inappropriate%20for%20many%20patients. [Accessed 18 October 2014].

5 Powles T, Catto James WF, Galsky Matthew D, Al-Ahmadie H, Meeks Joshua J, Nishiyama H, et al. Perioperative Durvalumab with Neoadjuvant Chemotherapy in Operable Bladder Cancer. *New England Journal of Medicine*. 0(0). Available from: https://doi.org/10.1056/NEJMoa2408154.

6 Memorial Sloan Kettering Cancer Center. *Powerful New Bladder Cancer Treatments: Antibody-Drug Conjugates and Checkpoint Inhibitors*. 2022. Available from: https://www.mskcc.org/news/who-can-be-helped-new-bladder-cancer-drugs-immunotherapy-and-antibody-drug-conjugates#antibody-drug-conjugates-deliver-a-precise-payload [Accessed 05 October 2024].

7 Powles T, Csőszi T, Özgüroğlu M, Matsubara N, Géczi L, Cheng SY, et al. Pembrolizumab alone or combined with chemotherapy versus chemotherapy as first-line therapy for advanced urothelial carcinoma (KEYNOTE-361): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(7):931-45. Available from: https://doi.org/10.1016/s1470-2045(21)00152-2.

8 Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee JL, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *N Engl J Med*. 2021;384(12):1125-35. Available from: https://doi.org/10.1056/NEJMoa2035807.

Copyright © National Institute for Health and Care Research Innovation Observatory, The University of Newcastle upon Tyne.

9 Rosenberg JE, O'Donnell PH, Balar AV, McGregor BA, Heath EI, Yu EY, et al. Pivotal Trial of Enfortumab Vedotin in Urothelial Carcinoma After Platinum and Anti-Programmed Death 1/Programmed Death Ligand 1 Therapy. *J Clin Oncol*. 2019;37(29):2592-600. Available from: https://doi.org/10.1200/jco.19.01140.

10 Yu EY, Petrylak DP, O'Donnell PH, Lee JL, van der Heijden MS, Loriot Y, et al. Enfortumab vedotin after PD-1 or PD-L1 inhibitors in cisplatin-ineligible patients with advanced urothelial carcinoma (EV-201): a multicentre, single-arm, phase 2 trial. *Lancet Oncol*. 2021;22(6):872-82. Available from: https://doi.org/10.1016/s1470-2045(21)00094-2.

11 Powles T, Valderrama Begoña P, Gupta S, Bedke J, Kikuchi E, Hoffman-Censits J, et al. Enfortumab Vedotin and Pembrolizumab in Untreated Advanced Urothelial Cancer. *New England Journal of Medicine*. 2024;390(10):875-88. Available from: https://doi.org/10.1056/NEJMoa2312117.

12 ClinicalTrials.gov. *Showing results for: Pembrolizumab + Enfortumab Vedotin*. Available from: https://clinicaltrials.gov/search?intr=Pembrolizumab%20%2B%20Enfortumab%20Vedotin%20&page=3 [Accessed 04 October 2024].

13 Cancer Research UK. *What is bladder cancer?* 2022. Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/about [Accessed 18 September 2024].

14 Cancer Research UK. *Types of bladder cancer*. 2022. Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/types-stages-grades/types [Accessed 18 September 2024].

15 American Society of Clinical Oncology. *First-Line Treatment of Cisplatin-Ineligible Patients With Metastatic Urothelial Carcinoma: The Pursuit of Improved Outcomes*. 2023. Available from: https://dailynews.ascopubs.org/do/first-line-treatment-cisplatin-ineligible-patients-metastatic-urothelial-carcinoma [Accessed 18 September 2024].

16 Cancer Research UK. *Risks and causes of bladder cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/risks-causes [Accessed 18 September 2024].

17 Cancer Research UK. *Symptoms of bladder cancer*. 2022. Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/symptoms [Accessed 18 September 2024].

18 Action Bladder Cancer UK. *The Facts About Bladder Cancer*. 2024. Available from: https://actionbladdercanceruk.org/the-facts-about-bladder-cancer/ [Accessed 18 September 2024].

19 Action Bladder Cancer UK. *Muscle-invasive bladder cancer*. 2019. Available from: https://actionbladdercanceruk.org/library/files/ABC%20UK%20MIBC%20FINAL%20WEB%20NOV%202019.pdf [Accessed 18 September 2024].

20 Office for National Statistics. *Cancer registration statistics, England*. 2017. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 18 September 2024].

21 Catto JWF, Mandrik O, Quayle LA, Hussain SA, McGrath J, Cresswell J, et al. Diagnosis, treatment and survival from bladder, upper urinary tract, and urethral cancers: real-world findings from NHS England between 2013 and 2019. *BJU International*. 2023;131(6):734-44. Available from: https://doi.org/https://doi.org/10.1111/bju.15970.

22 National Health Service (NHS). *Primary diagnosis: 3 character*. 2024. Available from: https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Ffiles.digital.nhs.uk%2FA5%2F5B8474%2Fhosp-epis-stat-admi-diag-2023-24-tab.xlsx&wdOrigin=BROWSELINK [Accessed 04 November 2024].

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23 Galsky MD, Hahn NM, Rosenberg J, Sonpavde G, Hutson T, Oh WK, et al. Treatment of patients with metastatic urothelial cancer "unfit" for Cisplatin-based chemotherapy. *J Clin Oncol*. 2011;29(17):2432-8. Available from: https://doi.org/10.1200/jco.2011.34.8433.

24 National Institute for Health and Care Excellence (NICE). *Bladder cancer: diagnosis and management*. 2015. Available from: https://www.nice.org.uk/guidance/ng2/resources/bladder-cancer-diagnosis-and-management-pdf-51036766405 [Accessed 04 October 2024].

25 National Institute for Health and Care Excellence (NICE). *Pembrolizumab [Specialist drug]*. 2024. Available from: https://bnf.nice.org.uk/drugs/pembrolizumab-specialist-drug/medicinal-forms/ [Accessed 04 November 2024].

26 National Institute for Health and Care Excellence (NICE). *Enfortumab vedotin [Specialist drug]*. 2024. Available from: https://bnf.nice.org.uk/drugs/enfortumab-vedotin-specialist-drug/medicinal-forms/ [Accessed 04 November 2024].

27 European Society for Medical Oncology (ESMO). *Bladder cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up*. 2024. Available from: https://www.annalsofoncology.org/action/showPdf?pii=S0923-7534%2821%2904827-4 [Accessed 18 October 2024].

28 European Society of Urology. *Muscle-invasive and Metastatic Bladder Cancer*. 2024. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Muscle-Invasive-and-Metastatic-Bladder-Cancer-2024.pdf [Accessed 18 October 2024].

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.

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