Health Technology Briefing
January 2024

Durvalumab and enfortumab vedotin with or without tremelimumab for muscle-invasive bladder cancer

Company/Developer	AstraZeneca UK

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 33623	NICE ID: N/A	UKPS ID: 670216

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Durvalumab and enfortumab vedotin with or without tremelimumab is currently in clinical development for patients with muscle invasive bladder cancer (MIBC), who are ineligible or refuse cisplatin therapy (a type of chemotherapy) and are receiving a radical cystectomy (removal of bladder and surrounding lymph nodes). 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. The current treatment option for patients with MIBC includes neoadjuvant (treatment given prior to main treatment, e.g., surgery) chemotherapy. 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. Therefore, alternative therapy options are required for this patient group.

Durvalumab is a type of protein (monoclonal antibody) that enhances the body's immune response to cancer cells. Tremelimumab is also a monoclonal antibody, that works by increasing production of immune cells which attack cancer cells. Enfortumab vedotin attaches to cancer cells and releases the drug inside the cells causing them to die. Enfortumab vedotin targets cancer cells more specifically as it binds to receptors which are expressed more on cancer cells than healthy cells. If licenced, durvalumab and enfortumab vedotin, with or without tremelimumab -would offer a treatment option to patients with MIBC who cannot receive cisplatin chemotherapy prior to radical cystectomy.

Proposed Indication

Neoadjuvant and adjuvant treatment of patients ineligible for cisplatin or who refuse cisplatin undergoing radical cystectomy for muscle invasive bladder cancer (MIBC).[1]

Technology

Description

Durvalumab (Imfinzi) is a human immunoglobulin G1 kappa (IgG1κ) monoclonal antibody that selectively blocks the interaction of programmed cell death ligand-1 (PD-L1) and CD80. Expression of PD-L1 protein is an adaptive immune response that helps tumours evade detection and elimination by the immune system. Selective blockade of PD-L1/PD-1 and PD-L1/CD80 interactions enhances antitumour immune responses and increases T-cell activation.[2] Tremelimumab (Imjudo) is a selective, fully human immunoglobulin G2 (IgG2) antibody that blocks cytotoxic T-lymphocyte-associated protein (CTLA-4) interaction with CD80 and CD86, thus enhancing T-cell activation and proliferation, resulting in increased T-cell diversity and enhanced antitumour activity.[3] Enfortumab vedotin 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 IgG1κ antibody conjugated to the microtubule-disrupting agent monomethyl auristatin E (MMAE) via a protease-cleavable maleimidocaproyl valine-citrulline linker. Release of MMAE disrupts the microtubule network within the cell, subsequently inducing cell cycle arrest and apoptotic cell death.[4]

Neoadjuvant and adjuvant durvalumab with enfortumab vedotin with or without tremelimumab is currently in phase III clinical development for patients with MIBC who are ineligible for cisplatin or who refuse cisplatin.[1] In the phase III trial VOLGA (NCT04960709), participants received either neoadjuvant durvalumab with tremelimumab and enfortumab vedotin followed by radical cystectomy and postoperative tremelimumab and durvalumab; or neoadjuvant durvalumab with enfortumab vedotin followed by radical cystectomy and postoperative durvalumab.[1]

Key Innovation

Dual checkpoint inhibition with durvalumab and tremelimumab may be superior to monotherapy as they may act synergistically.[5] As they both have different mechanisms of action, harnessing these different mechanisms in tandem via combination therapies has potential for greater antitumor effect compared with monotherapies.[6] Previous studies have also demonstrated enfortumab vedotin prolonged survival in patients with advanced urothelial carcinoma (UC).[7] In a pilot trial (NCT02812420) for the combination neoadjuvant treatment of durvalumab and tremelimumab for localised UC, there was a complete response rate of 37.5% and a downstaging of tumours in 58% of patients who completed surgery.[5]

Currently, there are no alternative neoadjuvant therapies to cisplatin for MIBC, meaning there is an unmet need for patients who are ineligible for cisplatin therapy or patients who refuse cisplatin therapy.[8] Potential benefits of neoadjuvant therapy include a chance of microscopic resection and, early eradication of micro metastases to prevent progression to metastatic disease. This can reduce tumour volume and has the benefit of converting a non-resectable tumour into a resectable tumour.[9] Adjuvant therapy (including chemotherapy, radiation therapy, hormone therapy, targeted therapy, and immunotherapy) has the potential to remove minimal residual disease and increase patient survival.[10] Therefore, if licensed, the combination of dual checkpoint inhibition (durvalumab and tremelimumab) with ADC (enfortumab vedotin) may provide further treatment options for patients with MIBC who are not eligible for standard cisplatin therapy.

Regulatory & Development Status

Durvalumab has Marketing Authorisation in EU/UK for the treatment of: [2]

- Non-small cell lung cancer (monotherapy)
- Small cell lung cancer (in combination)
- Biliary tract cancer (in combination)
- Hepatocellular carcinoma (in combination with durvalumab).

Tremelimumab has Marketing Authorisation in EU/UK for the treatment of hepatocellular carcinoma in combination with durvalumab.[3]

Enfortumab vedotin has Marketing Authorisation in the EU/UK as a monotherapy for 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.[3]

The combination of durvalumab, tremelimumab and enfortumab vedotin is not currently in any other phase II or III clinical trials.[3]

Patient Group

Disease Area and Clinical Need

MIBC is a cancer that spreads into the detrusor muscle of the bladder. The detrusor muscle is the thick muscle deep in the bladder wall.[11] MIBC has a higher likelihood of metastasising to other areas of the body.[12] Most MIBC originates from a dysplastic urothelium, evolving into a flat carcinoma in situ and finally into a high-grade non-invasive UC through the acquisition of cyclin-dependent kinase inhibitor 2A (CDKN2A) alterations, this leads to further genetic instability and eventually the accumulation of numerous genetic and epigenetic alterations.[13] Some symptoms of MIBC include; haematuria (blood in urine), frequent and urgent need to pass urine, pain when passing urine, pain in lower abdomen, and back pain.[11] There are certain risk factors associated with developing bladder cancer such as; smoking, exposure to chemicals such as benzidine and ortho-toluidine, treatments for other cancers such as radiotherapy for bowel cancer, chronic urinary tract infections, long-term bladder stones, use of pioglitazone for treating Type II diabetes, long-term use of indwelling catheters, and familial history.[12,14] Patients with MIBC may be ineligible for cisplatin treatment due to renal dysfunction, poor performance or other comorbidities such as neuropathy, hearing loss and heart failure.[15]

Between 2016-2018, bladder cancer was the 11th most common cancer in the UK, accounting for 3% of all new cancer cases.[16] In England in 2017, newly diagnosed registered cases of malignant neoplasms of bladder (ICD 10 code: C67) were 8,686 and directly age standardised incidence rate in males was 27.6 per 100,000 and in females was 8.2 per 100,000.[17] Approximately 1/3 of people diagnosed with bladder cancer have MIBC.[18] In England (2022-23) there were 66,634 finished consultant episodes (FCEs) and 62,831 admissions for neoplasm of the bladder, resulting in 41,531 day cases and 87,622 FCE bed days.[19] 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.[17] For patients diagnosed between 2013 and 2017, followed up to 2018, the 1-year and 5-year survival rates were 68.8% and 41.2% respectively.[17] Approximately 30-50% of patients are ineligible for cisplatin therapy.[20]

Recommended Treatment Options

Treatment for MIBC can include cystectomy, radiotherapy, chemotherapy and immunotherapy.[12] The treatment options recommended by NICE for MIBC patients ineligible for cisplatin include:[21]

- Radical cystectomy
- Radical radiotherapy
- Adjuvant chemotherapy after radical cystectomy

Clinical Trial Information

Trial	**VOLGA; NCT04960709, EudraCT 2020-005452-38;** A Phase III Randomized, Open-Label, Multicenter Study to Determine the Efficacy and Safety of Durvalumab in Combination With Tremelimumab and Enfortumab Vedotin or Durvalumab in Combination With Enfortumab Vedotin for Perioperative Treatment in Patients Ineligible for Cisplatin or Who Refuse Cisplatin Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer (VOLGA) **Phase III** - Recruiting **Locations:** 9 EU countries, UK, USA, and other countries **Primary completion date:** July 2025
Trial Design	Randomised, parallel assignment, open label, active comparator controlled
Population	N=830; 18 years or older; patients with histologically or cytologically confirmed muscle invasive UC of the bladder that have received no prior treatment for MIBC or bladder UC.
Intervention(s)	Participants will either receive: - 3 preoperative 21-day cycles of durvalumab + tremelimumab + enfortumab vedotin, followed by radical cystectomy, followed by 1 cycle of postoperative tremelimumab and 9 cycles of durvalumab. Each postoperative cycle is 28 days. - 3 preoperative 21-day cycles of durvalumab + enfortumab vedotin, followed by radical cystectomy, followed by 9 cycles of durvalumab. Each postoperative cycle is 28 days.
Comparator(s)	Cystectomy with or without approved adjuvant therapy (nivolumab)
Outcome(s)	Primary outcome measure: • Pathological complete response rate [Time frame: 3 years] • Event-free survival [Time frame: 3 years] • Frequency of Adverse Events [Time frame: at study completion and at 3 months] • Safety and tolerability of durvalumab + tremelimumab + enfortumab vedotin in participants with MIBC who are ineligible for cisplatin or who refuse cisplatin [Time frame: up to 84 months] • Changes in WHO/ Eastern Cooperative Oncology Group (ECOG) performance status [Time frame: up to 84 months] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Durvalumab is marketed in the UK for treatment of non-small cell lung cancer, the NHS indicative price for 500mg per 10ml-infusion vial is £2466.[22]

The cost of tremelimumab is not yet known.
Enfortumab vedotin is market in the UK for treatment of UC, 1 vial containing 20mg of enfortumab vedotin is £578, 1 vial containing 30mg of enfortumab vedotin is £867.[23]

Relevant Guidance

NICE Guidance

- 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 technology appraisal in development. Nivolumab with BMS-986205 and chemotherapy or neoadjuvant treatment of muscle-invasive bladder cancer (GID-TA11115). Expected date of issue 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
- 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

- Witjes et al. European Association of Urology Guidelines: Muscle-invasive and Metastatic Bladder Cancer. 2023.[24]
- Powles et al. European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow up of Bladder Cancer. 2021.[25]

Additional Information

References

1 ClinicalTrials.gov. *A Phase III Randomized, Open-Label, Multicenter Study to Determine the Efficacy and Safety of Durvalumab in Combination With Tremelimumab and Enfortumab Vedotin or Durvalumab in Combination With Enfortumab Vedotin for Perioperative Treatment in Patients Ineligible for Cisplatin or Who Refuse Cisplatin Undergoing Radical Cystectomy for Muscle Invasive Bladder Cancer (VOLGA). Trial ID: NCT04960709*. 2021. Status: Recruiting Available from: https://clinicaltrials.gov/study/NCT04960709?term=NCT04960709&rank=1#study-overview [Accessed 04 October 2023].

2 Electronic Medicines Compendium. *Imfinzi 50 mg/mL concentrate for solution for infusion* 21 September 2018. Available from: https://www.medicines.org.uk/emc/product/9495#PHARMACOKINETIC_PROPS [Accessed 04 October 2023].

3 Electronic Medicines Compendium. *IMJUDO 20 mg/ml concentrate for solution for infusion*. 2023. Available from: https://www.medicines.org.uk/emc/product/14841 [Accessed 04 October 2023].

4 Electronic Medicines Compendium. *Padcev 20 mg powder for concentrate for solution for infusion*. 2022. Available from: https://www.medicines.org.uk/emc/product/13669/smpc [Accessed 04 October 2023].

5 Singh A, Osbourne AS, Koshkin VS. Perioperative Immunotherapy in Muscle-Invasive Bladder Cancer. *Current Treatment Options in Oncology*. 2023;24(9):1213-30. Available from: https://doi.org/10.1007/s11864-023-01113-z.

6 Chhaya S, Watts I, Ng K, Mustapha R, Powles T, Sharma A, et al. Role of Perioperative Immune Checkpoint Inhibitors in Muscle Invasive Bladder Cancer. *Oncology and Therapy*. 2023;11(1):49-64. Available from: https://doi.org/10.1007/s40487-022-00218-z.

7 Powles T, Rosenberg JE, Sonpavde GP, Loriot Y, Durán I, Lee J-L, et al. Enfortumab Vedotin in Previously Treated Advanced Urothelial Carcinoma. *New England Journal of Medicine*. 2021;384(12):1125-35. Available from: https://doi.org/10.1056/NEJMoa2035807.

8 Gao J, Navai N, Alhalabi O, Siefker-Radtke A, Campbell MT, Tidwell RS, et al. Neoadjuvant PD-L1 plus CTLA-4 blockade in patients with cisplatin-ineligible operable high-risk urothelial carcinoma. *Nature Medicine*. 2020;26(12):1845-51. Available from: https://doi.org/10.1038/s41591-020-1086-y.

9 Osanto S, Álvarez Gómez de Segura C. Neoadjuvant and adjuvant treatments in muscle-invasive bladder cancer: Where are we? *Arch Esp Urol*. 2020;73(10):971-85. https://pubmed.ncbi.nlm.nih.gov/33269716/.

10 Dong P, Gewirtz DA. Editorial: Risks and Benefits of Adjuvants to Cancer Therapies. *Frontiers in Oncology*. 2022;12. Available from: https://doi.org/10.3389/fonc.2022.913626.

11 Urology Care Foundation, American Urological Association. *What is Muscle Invasive Bladder Cancer (MIBC)?* 2020. Available from: https://www.urologyhealth.org/urology-a-z/m/muscle-invasive-bladder-cancer#More%20Information [Accessed 06 October 2023].

12 National Health Service. *Bladder Cancer*. 2021. Available from: https://www.nhs.uk/conditions/bladder-cancer/ [Accessed 06 October 2023].

13 Mohanty SK, Lobo A, Mishra SK, Cheng L. Precision Medicine in Bladder Cancer: Present Challenges and Future Directions. *Journal of Personalized Medicine*. 2023.

14 Cancer Research UK. *Risks and causes of bladder cancer*. 2023. Available from: https://www.cancerresearchuk.org/about-cancer/bladder-cancer/risks-causes [Accessed 06 October 2023].

15 Balar AV, Castellano D, O'Donnell PH, Grivas P, Vuky J, Powles T, et al. First-line pembrolizumab in cisplatin-ineligible patients with locally advanced and unresectable or metastatic urothelial cancer (KEYNOTE-052): a multicentre, single-arm, phase 2 study. *The Lancet Oncology*. 2017;18(11):1483-92. Available from: https://doi.org/https://doi.org/10.1016/S1470-2045(17)30616-2.

16 Cancer Research UK. *Bladder cancer statistics*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bladder-cancer?_gl=1*1faw65x*_gcl_au*MTcxNjU4MTYwNC4xNjk2NTg1MDU4*_ga*NTM3NzMzMjUwLjE2OTY1ODUwNDY.*_ga_58736Z2GNN*MTY5NjU5MTg5OC4yLjEuMTY5NjU5MzA4OS4wLjAuMA..&_ga=2.152741169.944710219.1696585046-537733250.1696585046#heading-Zero [Accessed 06 October 2023].

17 Office for National Statistics. *Cancer registration statistics, England*. 2019. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/cancerregistrationstatisticscancerregistrationstatisticsengland [Accessed 06 October 2023].

18 Action Bladder Cancer UK. *A short guide to MIBC*. Available from: https://actionbladdercanceruk.org/library/files/ABC%20UK%20MIBC%20FINAL%20WEB%20NOV%202019.pdf [Accessed 16 November 2023].

19 National Health Service. *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 06 October 2023].

20 Galsky MD, Hahn NM, Rosenberg J, Sonpavd G, Hutson T, Oh WK, et al. Treatment of Patients With Metastatic Urothelial Cancer "Unfit" for Cisplatin-Based Chemotherapy. *Journal of Clinical Oncology*. 2011;29(17). https://www.cccnevada.com/dashboard/wp-content/uploads/Vogelzang-Treatment-of-Patients.pdf.

21 National Institute for Health and Care Excellence. *Bladder cancer: diagnosis and management*. 2015. Available from: https://www.nice.org.uk/guidance/ng2/chapter/1-Recommendations#treating-muscle-invasive-bladder-cancer-2 [Accessed 06 October 2023].

22 National Institute for Health and Care Excellence *Durvalumab [Specialist drug] Medicinal forms*. Available from: https://bnf.nice.org.uk/drugs/durvalumab-specialist-drug/medicinal-forms/ [Accessed 16 November 2023].

23 National Institute for Health and Care Excellence. *Enfortumab vedotin [Specialist drug]*. 2023. Available from: https://bnf.nice.org.uk/drugs/enfortumab-vedotin-specialist-drug/ [Accessed 04 October 2023].

24 Witjes JA, Bruins HM, Carrión A, Cathomas R, E.M. Compérat, Efstathiou JA, et al. *EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer*. Available from: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-Guidelines-on-Muscle-Invasive-Bladder-Cancer-2023_2023-03-14-145913_jsen.pdf [Accessed 06 October 2023].

25 Powles T, Bellmunt J, Comperat E. *Bladder Cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up*. 2021. Available from: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-genitourinary-cancers/bladder-cancer [Accessed 06 October 2023].

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.