

Health Technology Briefing October 2023

Pembrolizumab and chemoradiation for treating muscle-invasive, non-metastatic bladder cancer

Company/Developer

Merck Sharp & Dohme Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 29289

NICE TSID: Not applicable

UKPS ID: 659332

Licensing and Market Availability Plans

Pembrolizumab and chemoradiation is currently in phase III trials.

Summary

Pembrolizumab in combination with chemoradiation is currently in clinical development for muscle-invasive, non-metastatic bladder cancer in adults. Bladder cancer occurs when a tumour develops in the bladder lining and if the cancer grows into a deeper, muscular layer of the bladder; this is known as muscle-invasive bladder cancer. The most common symptom of the condition is blood in the urine, though other symptoms include urinating more often, having a sudden urge to urinate or having a burning sensation while urinating. Risk factors for developing bladder cancer include smoking and being exposed to industrial chemicals. Bladder cancer can take a long time to develop, so it is more common in older people. There are currently limited treatment options for people with muscle-invasive, non-metastatic bladder cancer.

Pembrolizumab is administered intravenously and works by binding to specific receptors, blocking their interaction with ligands. In turn, this enhances the responses of specific cells in the body, including anti-tumour cells. If licensed, the use of pembrolizumab alongside chemoradiation could provide another treatment option for people with muscle-invasive, non-metastatic bladder cancer.

Proposed Indication

Treatment of muscle-invasive, non-metastatic bladder cancer in adults.¹

Technology

Description

Pembrolizumab (Keytruda) is a humanised monoclonal antibody that binds to programmed cell death-1 receptors, blocking their interactions with programmed death ligand (PD-L)-1 and PD-L2. As the programmed death 1 (PD-1) receptor has been shown to be involved in the control of T-cell immune responses, pembrolizumab is designed to enhance T-cell responses, including anti-tumour responses, by blocking PD-1 that binds to PD-L1 and PD-L2, which may both be expressed in tumours.²

Pembrolizumab in combination with chemoradiation is in clinical development for treating muscle-invasive, non-metastatic bladder cancer in adults. A phase III trial is assessing the effectiveness of pembrolizumab (400 mg administered intravenously once every six weeks) and an investigator's choice of one of three chemoradiation regimens versus placebo and an investigator's choice of one of three chemoradiation regimens in adults with muscle-invasive, non-metastatic bladder cancer (KEYNOTE-992; NCT04241185).¹

Key Innovation

There are currently three options for treating muscle-invasive, non-metastatic bladder cancer. The National Institute for Health and Care Excellence (NICE) recommends: neoadjuvant chemotherapy; radical cystectomy (complete removal of the bladder) or radical radiotherapy; and an adjuvant cisplatin combination chemotherapy after radical cystectomy.³ Pembrolizumab is already licensed in the EU/UK for a number of different indications and has proven to be a promising treatment for high-risk non-muscle invasive bladder cancer in a phase II trial (KEYNOTE-057, [NCT02625961](#)).^{2,4} If licensed, the combination of pembrolizumab and chemoradiation would offer people with muscle-invasive, non-metastatic bladder cancer another potential treatment option.

Regulatory & Development Status

Pembrolizumab currently has Marketing Authorisation in the UK as a combination therapy for:²

- non-small cell lung cancer (NSCLC)
- head and neck squamous cell carcinoma (HNSCC)
- renal cell carcinoma (RCC)
- oesophageal carcinoma
- triple-negative breast cancer (TNBC)
- endometrial carcinoma
- cervical cancer

Pembrolizumab currently has Marketing Authorisation in the UK as a monotherapy for:²

- melanoma
- NSCLC
- classic Hodgkin lymphoma (cHL)
- urothelial carcinoma
- HNSCC
- RCC
- microsatellite instability high (MSI-H) or mismatch repair deficient (DMMR) cancers (including colorectal cancer, advanced or recurrent endometrial carcinoma and unresectable or metastatic gastric, small intestine or biliary cancer)

- TNBC (as adjuvant treatment after surgery)

Pembrolizumab is in phase II and III clinical trials for multiple indications including, but not limited to:⁵

- solid tumours
- Merkel cell carcinoma
- NSCLC
- melanoma
- solid tumour or lymphoma
- brain metastasis

Patient Group

Disease Area and Clinical Need

Bladder cancer is a condition where a tumour develops in the bladder lining.⁶ The most common symptom of bladder cancer is blood in the urine, though other, less common symptoms include a need to urinate more frequently, sudden urges to urinate or having a burning sensation when urinating. If the bladder cancer reaches a more advanced stage, symptoms can include pelvic pain, bone pain, unintentional weight loss and swelling of the legs.⁷ If the cancer grows into a deeper, muscular layer of the bladder or beyond, this is known as muscle-invasive bladder cancer.⁸ If bladder cancer becomes muscle-invasive, it requires more intense treatment as there is a risk it could spread to other parts of the body.⁸ Risk factors for bladder cancer include smoking, exposure to industrial chemicals, radiotherapy to treat previous cancers close to the bladder (e.g. bowel cancer), previous treatment with certain chemotherapy medications, certain treatments for type 2 diabetes, having a tube in the bladder (an indwelling catheter) for a long amount of time, long-term or repeated urinary tract infections, long-term bladder stones, and having an untreated infection called schistosomiasis (bilharzia; caused by a parasite that lives in fresh water and is very rare in the UK).⁹ As bladder cancer takes a long time to develop, it is most common in older people; almost 60% of new cases of the condition are diagnosed in people aged 75 and over.¹⁰

It is estimated that about 10,000 people in the UK are diagnosed with bladder cancer.⁶ It is the 11th most common cancer in the UK and the 8th most common in men.¹⁰ In England in 2021-22, there were 46,634 finished consultant episodes (FCE) and 43,647 admissions for bladder cancer (ICD10 code C67.9), which resulted in 63,143 FCE bed days and 28,638 day cases.¹¹

Recommended Treatment Options

NICE currently recommends the following treatment options for muscle-invasive, non-metastatic bladder cancer.³

- Neoadjuvant chemotherapy with a cisplatin-based regimen for newly diagnosed muscle-invasive urothelial bladder cancer.
- Radical cystectomy or radiotherapy with a radiosensitiser for people with muscle-invasive urothelial bladder cancer for whom radical therapy is suitable.
- Adjuvant cisplatin combination chemotherapy after radical cystectomy for those whom neoadjuvant chemotherapy was unsuitable.

Clinical Trial Information

Trial

KEYNOTE-992, [NCT04241185](#), [EudraCT- 2019-004023-20](#); A Phase 3, Randomized, Double-blind, Placebo-controlled Clinical Trial to Study the

	<p>Efficacy and Safety of Pembrolizumab (MK-3475) in Combination With Chemoradiotherapy (CRT) Versus CRT Alone in Participants With Muscle-invasive Bladder Cancer (MIBC) (KEYNOTE-992) Phase III – Recruiting Location(s) – UK, 11 EU countries, USA and other countries Study completion date (estimated): June 2031</p>
Trial Design	Randomised, parallel-assignment, quadruple-blind, placebo-controlled
Population	N = 636 (estimated); adults aged 18 and over with histologically-confirmed diagnosis of muscle-invasive, non-metastatic bladder cancer and eligible to receive one of the protocol-specified radiosensitising chemotherapy regimens.
Intervention(s)	400 mg of intravenous pembrolizumab once every six weeks plus one of three chemotherapy regimens as chosen by the investigator.
Comparator(s)	Intravenous placebo to pembrolizumab administered once every six weeks plus one of three chemotherapy regimens chosen by the investigator.
Outcome(s)	<p>Primary outcome measure: Bladder intact event-free survival (BI-EFS) [Time Frame: Up to approximately 71 months]</p> <p>See trial record for full list of other outcomes.</p>
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK for several cancer indications. The cost of pembrolizumab 100mg/4ml (25 mg per 1 ml) solution for infusion vial is £2630 (hospital only).¹²

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 for neoadjuvant treatment of muscle-invasive bladder cancer (GID-TA11336). Expected date of issue to be confirmed.
- 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. Enfortumab vedotin with pembrolizumab for neoadjuvant and adjuvant treatment of cisplatin-eligible muscle-invasive bladder cancer (GID-TA11338). Expected date of issue to be confirmed.
- NICE clinical guideline. Bladder cancer: diagnosis and management (NG2). February 2015.
- NICE quality standard. Bladder cancer (QS106). December 2015.

NHS England (Policy/Commissioning) Guidance

- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. 16033/P. July 2016.
- NHS England. Service specification: Specialised kidney, bladder and prostate cancer services (Adults). 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

- Witjes JA, Bruins HM, Carrión A, Cathomas R, Compérat EM, Efstathiou JA, et al. *EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer*. 2023.¹³
- 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. 2022.¹⁴
- Flaig TW, Spiess PE, Agarwal N, Boorjian SA, Buyyounouski MK, Chang S, et al. Bladder Cancer, Version 3.2020, NCCN Clinical Practice Guidelines in Oncology. 2020.¹⁵
- Chang SS, Bochner BH, Chou R, Dreicer R, Kamat AM, Lerner SP, et al. Treatment of Non-Metastatic Muscle-Invasive Bladder Cancer: AUA/ASCO/ASTRO/SUO Guideline. 2017.¹⁶

Additional Information

References

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- 2 electronic medicines compendium (emc). *KEYTRUDA 25 mg/mL concentrate for solution for infusion*. 2023. Available from: <https://www.medicines.org.uk/emc/product/2498/smpc> [Accessed 3 August 2023].
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