

Health Technology Briefing August 2022

Pembrolizumab perioperative therapy with neoadjuvant chemotherapy for treating cisplatin eligible muscle-invasive bladder cancer

Company/Developer

Merck Sharp & Dohme Ltd

New Active Substance

Significant Licence Extension (SLE)

NIHRIO ID: 27175

NICE TSID: 10602

UKPS ID: 659330

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab perioperative (preoperative and postoperative) therapy in combination with neoadjuvant (before surgery) chemotherapy is in development for the treatment of patients with cisplatin eligible muscle invasive bladder cancer (MIBC). MIBC is when the cancer has spread beyond the lining of the bladder and into the muscle layer. The most well-known risk factor for MIBC is smoking. The most common symptom of MIBC is blood in the urine. The main treatment option is a radical cystectomy, a surgery where parts or all of the bladder is removed. Therefore, other treatment approaches with long disease control excluding surgery are needed.

Pembrolizumab is a type of protein (monoclonal antibody) that is administered intravenously and has been designed to increase the immune system's ability to kill cancer cells. Pembrolizumab is mainly used in adults for cancers that are advanced, have spread to other parts of the body (metastatic) or are not responding to other treatments. If licensed, pembrolizumab in combination with chemotherapy will offer an alternative treatment option for adults with cisplatin eligible MIBC.

Proposed Indication

For the treatment of adults with cisplatin eligible muscle-invasive bladder cancer (MIBC).¹

Technology

Description

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.^{2,3}

Pembrolizumab perioperative therapy in combination with neoadjuvant chemotherapy is currently in phase III clinical development for adult patients with cisplatin eligible MIBC. In the phase III clinical trial (KEYNOTE-866; NCT03924856), 4 preoperative cycles of 200mg of pembrolizumab is administered intravenously in combination with gemcitabine plus cisplatin, followed by surgery, followed by up to 13 cycles of postoperative pembrolizumab also administered by intravenous (IV) infusion.¹

Key Innovation

Currently, the recommended standard of care for MIBC is radical cystectomy (RC) with bilateral pelvic lymph node dissection, preceded by the administration of neoadjuvant chemotherapy in patients who are eligible to receive cisplatin chemotherapy.^{4,5} However, neoadjuvant chemotherapy is not a widely used treatment for MIBC, as it is administered in only 20% of eligible patients. In a recent study, a high proportion of PD-L1-positive patients with MIBC treated with neoadjuvant pembrolizumab have shown pathologic complete response.⁵ Therefore, if licensed, perioperative pembrolizumab in combination with neoadjuvant chemotherapy may provide a promising clinical benefit and offer an important alternative to existing therapies, including radical cystectomy.

Regulatory & Development Status

Pembrolizumab as a monotherapy or in combination with various medicinal products is currently licensed in the UK for the following indications:^{3,6}

- Melanoma
- Non-small cell lung carcinoma
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma (RCC)
- Oesophageal carcinoma
- Colorectal cancer
- Triple negative breast cancer
- Endometrial carcinoma (EC)
- Cervical cancer
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancer located in colorectal cancer, endometrial carcinoma, gastric cancer, small intestine cancer, and biliary cancer

Pembrolizumab in combination with chemotherapy is currently in phase II and phase III clinical development for the treatment of various types of cancer which include:⁷

- Locally advanced esophagogastric junction adenocarcinoma
- Pancreatic cancer
- Non-small cell lung cancer
- Head and neck squamous cell carcinoma
- Ovarian cancer

Patient Group

Disease Area and Clinical Need

Bladder cancer is the growth of cancerous cells within the bladder. If the growth of these cells is contained within the lining of the bladder, this is described as non-muscle-invasive bladder cancer (NMIBC), whereas if the cells spread beyond the lining into the surrounding bladder muscle, this is MIBC.⁸ Most cases of bladder cancer appear to be caused by exposure to harmful substances, which lead to abnormal changes in the bladder's cells over many years. Contact with certain chemicals previously used in manufacturing is also known to cause bladder cancer. However, these substances have since been banned. Tobacco smoke is a common cause and it's estimated that more than 1 in 3 cases of bladder cancer are caused by smoking.⁸ Tobacco smoking is the most well-established risk factor, causing 50–65% of male cases and 20–30% of female cases.⁹ The most common symptom of bladder cancer is blood in urine also known as haematuria. Other symptoms of bladder cancer include pelvic pain, bone pain, unintentional weight loss, and swelling of the legs.¹⁰

In England in 2017, there were 8,686 new registrations for malignant neoplasm of bladder (ICD-10 code C67).¹¹ The 2020-2021 Hospital Episodes Statistics for England recorded a total of 56,069 finished consultant episodes (FCE) for malignant neoplasm of bladder, resulting in 52,437 hospital admissions, 73,087 FCE bed days and 30,679 day cases.¹²

Recommended Treatment Options

The current treatment options recommended by NICE for adults with MIBC are:¹³

- Neoadjuvant chemotherapy for newly diagnosed muscle-invasive urothelial bladder cancer
- Radical therapy
- RC
- Adjuvant chemotherapy after radical therapy for muscle-invasive or lymph-node-positive urothelial bladder cancer
- Radical radiotherapy

Clinical Trial Information

Trial

KEYNOTE-866; [NCT03924856](#); [Eudra CT2018-003808-39](#); A Phase 3, Randomized, Double-blind Study to Evaluate Perioperative Pembrolizumab (MK-3475) + Neoadjuvant Chemotherapy Versus Perioperative Placebo + Neoadjuvant Chemotherapy in Cisplatin-eligible Participants With Muscle-invasive Bladder Cancer (KEYNOTE-866)

Phase III: Recruiting

Location(s): 10 EU countries, UK, USA, Canada and other countries

Primary completion date: June 2025

Trial Design	Randomised, quadruple, double-blind, parallel assignment
Population	N=870 (estimated); subjects aged 18 and over with histologically confirmed diagnosis of urothelial carcinoma (UC) / MIBC (T2-T4aN0M0 or T1-T4aN1M0) with predominant ($\geq 50\%$) urothelial histology
Intervention(s)	4 preoperative cycles of 200mg of pembrolizumab on day 1 of each 21-day cycle plus gemcitabine 1,000mg/ m ² , IV infusion on Days 1 and 8 of each 21-day cycle plus 70mg /m ² cisplatin, followed by surgery, followed by up to 13 cycles of postoperative pembrolizumab by IV
Comparator(s)	4 preoperative cycles of placebo to pembrolizumab PLUS gemcitabine PLUS cisplatin, followed by surgery, followed by up to 13 cycles of postoperative placebo to pembrolizumab
Outcome(s)	Pathologic Complete Response (pCR) Rate [Time Frame: Up to approximately 15 Weeks (Time of surgery)] Event-Free Survival (EFS) [Time Frame: Up to approximately 71 months] See trial record for full list of all outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a 100mg/4ml vial costs £2,630.00.¹⁴

Relevant Guidance

NICE Guidance

- NICE guidance in development. Nivolumab for treating resected high-risk invasive urothelial cancer (GID-TA 10742). August 2022.
- NICE guidance. Bladder cancer: diagnosis and management (NG2). Feb 2015.
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NHS England (Policy/Commissioning) Guidance

- NHS England. Guidelines for the Management of Bladder Cancer. December 2016.
- NHS England. Clinical Commissioning Policy: Robotic Assisted Surgery for Bladder Cancer. July 2016. 16033/P.
- 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

- European Association of Urology (EAU). EAU Guidelines on Muscle-invasive and Metastatic Bladder Cancer. 2022⁹

- Powles T, Bellmunt J, Comperat E, et al., Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. 2021¹⁵

Additional Information

References

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