Health Technology Briefing
March 2024

Pembrolizumab adjuvant for urothelial carcinoma and/or localised muscle invasive bladder cancer

Company/Developer	Merck, Sharp and Dohme

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 38268	NICE ID: N/A	UKPS ID: 673570

Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Pembrolizumab is currently in clinical development for patients with localised muscle-invasive bladder cancer (MIBC) (where the cancer has grown into, but not through the muscle layer of the bladder) or and/or urothelial cancer (UC) which has spread from where it started to nearby tissue or lymph nodes (locally advanced), who are ineligible or refuse cisplatin therapy (a type of chemotherapy) and have received a radical cystectomy (removal of bladder and surrounding lymph nodes). The survival rates for patients with MIBC and locally advanced UC 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 adjuvant (treatment given after 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.

Pembrolizumab is a type of protein (monoclonal antibody) that enhances the body's immune response to cancer cells. Immune cells have a receptor on their surface called PD-1, some cancers can make a protein called PD-L1 which is able to bind to this receptor and stops the immune cells working. This allows cancer cells to grow and multiply without being killed by the immune cells. Pembrolizumab blocks the PD-1 receptors which prevents cancer cells switching off these cells. This increases the immune systems ability to kill cancer cells. If licensed, pembrolizumab would offer an alternative adjuvant therapy for patients ineligible or who refuse cisplatin treatment following radical cystectomy.

Proposed Indication

Adjuvant treatment for patients with localised muscle-invasive bladder cancer (MIBC) or locally advanced urothelial cancer (UC).[1]

Technology

Description

Pembrolizumab (KEYTRUDA, BCD-201, lambrolizumab, MK-3475, pembrolizumab biosimilar BCD-201 SCH 900475) 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.[1,2] 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]

Adjuvant pembrolizumab is in phase III clinical development for patients with localised MIBC or locally advanced UC.[1] In the phase III trial AMBASSADOR (NCT03244384), participants received pembrolizumab intravenous (IV, given through injection into the vein) for 30 minutes every 21 days for up to 18 cycles.[1]

Key Innovation

Adjuvant therapy (including chemotherapy, radiation therapy, hormone therapy, targeted therapy, and immunotherapy) has the potential to remove micrometastases and increase patient survival.[3,4] Between 20-50% of patients with MIBC are ineligible for cisplatin therapy, which may be due to renal dysfunction, poor performance or other comorbidities such as neuropathy, hearing loss and heart failure.[5,6] Standard of care for these patients is radical cystectomy followed by pelvic lymph node dissection.[6] These patients experience high rates of disease recurrence, which can be up to 50%.[6] Adjuvant treatment with pembrolizumab may reduce the risk of micrometastases following radical cycetomy.[3] A phase II study, KEYNOTE-052 (NCT02335424), showed that pembrolizumab provided meaningful, antitumour activity in cisplatin ineligible patients at 5-year follow up.[7] The phase III trial MK-3475-045/KEYNOTE-045 (NCT02256436) showed pembrolizumab is associated with longer overall survival (by approximately three months) and has fewer treatment-related adverse events when compared with chemotherapy as a second-line treatment for advanced UC.[8]

There is an unmet need for patients who are ineligible for adjuvant cisplatin treatment or who refuse cisplatin treatment. If licensed, adjuvant pembrolizumab may provide an alternative treatment option for these patients.

Regulatory & Development Status

Pembrolizumab has Marketing Authorisation in UK/EU as monotherapy for:[2,9]

- Melanoma
- Non-small cell lung cancer
- Urothelial carcinoma
- Classical Hodgkin lymphoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Colorectal cancer
- Oesophageal carcinoma
- Breast cancer
- Endometrial carcinoma

- Cervical cancer
- Gastric cancer
- Small intestine cancer
- Biliary cancer

Pembrolizumab is currently in phase II/III clinical development for melanoma, non-small cell lung cancer, classical Hodgkin lymphoma, head and neck cancer, renal cell carcinoma, colorectal cancer, oesophageal carcinoma, breast cancer, endometrial carcinoma, cervical cancer, gastric cancer, and urothelial carcinoma.[10]

Patient Group

Disease Area and Clinical Need

UC arises from malignant transformation of the cells that line the urinary tract.[11] As UC disease advances it can spread into the detrusor muscle of the bladder, becoming MIBC.[12] MIBC can also metastasize to other areas of the body through the lymphatic system.[13] 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.[14] Some symptoms of advanced UC and MIBC can include: haematuria (blood in urine), frequent and urgent need to pass urine, pain when passing urine, pain in lower abdomen, and back pain.[11,15] 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.[13,16]

Between 2016-2018, bladder cancer was the 11th most common cancer in the UK, accounting for 3% of all new cancer cases.[17] In England in 2017, there were 8,686 newly diagnosed registered cases of malignant neoplasms of bladder (ICD 10 code: C67) and the direct age standardised incidence rates were 27.6 and 8.2 per 100,000 in males and females respectively.[18] UC accounts for approximately 90% of all bladder cancers in the UK.[19] Approximately 25% of bladder cancers are MIBC, and 5% of bladder cancers metastasise to surrounding tissues such as lymph nodes, or distal sites such as the lungs.[20] Approximately 30-50% of patients are ineligible for cisplatin therapy.[21] 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.[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.[18] 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.[18]

Recommended Treatment Options

The following adjuvant treatments are recommended by the National Institute for Health and Care Excellence (NICE) for UC and/or MIBC:

- Nivolumab for muscle invasive UC that is at high risk of recurrence after radical resection in adults whose tumours express PD-L1 at a level of 1% or more. Only if adjuvant treatment with platinum-based chemotherapy is unsuitable and the company provides it according to the commercial arrangement.[23]

- Adjuvant cisplatin combination chemotherapy after radical cystectomy for people with a diagnosis of muscle-invasive or lymph-node-positive urothelial bladder cancer for whom neoadjuvant chemotherapy was not suitable (muscle invasion was not shown on biopsies before cystectomy).[24]

Clinical Trial Information

Trial	**AMBASSADOR**; NCT03244384; Phase III randomized Adjuvant Study of Pembrolizumab in muscle invasive and locally advanced urothelial carcinoma (AMBASSADOR) Versus Observation **Phase III** - Ongoing **Location(s):** United States, Guam **Primary completion date:** July 2025
Trial Design	Randomised, parallel assignment, open label
Population	N=739 (estimated); 18 years or older; patients with histologically confirmed muscle-invasive urothelial carcinoma of the bladder, urethra, upper tract, or lymph node positive (LN+) disease. Patients must have either; received neoadjuvant chemotherapy, must not be cisplatin eligible or decline adjuvant cisplatin or other systemic chemotherapy.
Intervention(s)	Participants will receive pembrolizumab IV for 30 mins every 21 days for up to 18 cycles in the absence of disease progression or unacceptable toxicity.
Comparator(s)	Observation. Patients undergo a CT scan, CT urography, and/or MRI throughout the trial. Patients may also undergo a cystoscopy and blood sample collection during screening and on study.
Outcome(s)	Primary outcome measure: • Overall survival [Time frame: 5 years] • Disease free survival [Time frame: 5 years] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The list price of pembrolizumab is £2,630.00 per 100mg vial.[25]

Relevant Guidance

NICE Guidance

- NICE Technology appraisal. Pembrolizumab with chemotherapy for neoadjuvant and adjuvant treatment of cisplatin-eligible muscle-invasive bladder cancer. (TA4064). Expected date of issue to be confirmed.

- NICE Technology appraisal. Enfortumab vedotin with pembrolizumab for neoadjuvant and adjuvant treatment of cisplatin-eligible muscle-invasive bladder cancer. (TA10718). Expected date of issue to be confirmed.
- NICE Technology appraisal. Durvalumab for neoadjuvant and adjuvant treatment of muscle-invasive bladder cancer. (TA10554). Expected date of issue to be confirmed.
- Durvalumab with enfortumab vedotin for neoadjuvant and adjuvant treatment of muscle-invasive bladder cancer when cisplatin is unsuitable. (TA11517). Expected date of issue to be confirmed.
- NICE Technology appraisal. Nivolumab for adjuvant treatment of invasive urothelial cancer at high risk of recurrence. (TA817). August 2022.
- 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.[26]
- Powles et al. European Society for Medical Oncology Clinical Practice Guidelines for diagnosis, treatment and follow up of Bladder Cancer. 2021.[27]

Additional Information

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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.