Health Technology Briefing
February 2023

Pembrolizumab with Bacillus Calmette-Guerin for treating high-risk non-muscle invasive bladder cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 26989	NICE ID: 10404	UKPS ID: 655493

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Pembrolizumab in combination with Bacillus Calmette-Guerin (BCG) is in development for the treatment of high-risk non-muscle invasive bladder cancer (NMIBC) that is recurrent or persistent following BCG induction or naïve to BCG treatment. Bladder cancer is when cancerous cells develop in the lining of the bladder. NMIBC is the most common type of bladder cancer and is categorised by risk. High-risk NMIBC is when cancerous cells are likely to persist or return after treatment, this means people with this type might require additional treatment and monitoring. Current treatment for patients with high-risk NMIBC is surgery to remove the bladder and intravesical (through a catheter) BCG treatment. NMBIC recurrence rate is high when treated with BCG alone, and surgical removal of the bladder is an invasive procedure.

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 and slow down the progression of the disease. If licenced, pembrolizumab in addition to BCG will offer an additional treatment option for adults with high-risk NMIBC that is recurrent or persistent following BCG induction or naïve to BCG treatment.

Proposed Indication

For the treatment of high-risk non-muscle invasive bladder cancer (NMIBC) that is recurrent or persistent following Bacillus Calmette-Guerin (BCG) induction or naïve to BCG treatment in adults.[1]

Technology

Description

Pembrolizumab (Keytruda) is a humanised monoclonal antibody which binds to the programmed cell death1 (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 maybe expressed by tumours or other cells in the tumour microenvironment.[2]

Pembrolizumab in combination with BCG is currently in phase III clinical development for treatment of adult patients with high-risk, NMIBC that is recurrent or persistent following BCG induction or naïve to BCG treatment. In the phase III trial (NCT03711032), participants received BCG in combination with 200 mg pembrolizumab administered intravenously (IV) every 3 weeks for 35 doses, or 400 mg pembrolizumab administered IV every 6 weeks for 9 doses.[1]

Key Innovation

Patients with high-risk NMIBC often experience a poor prognosis with a high chance of progression, and metastasis. In addition to experiencing a reduced quality of life.[3] An interim analysis of an open-label phase II study of pembrolizumab monotherapy in patients with BCG-unresponsive NMIBC, showed that pembrolizumab demonstrated encouraging anti-tumour activity and durable response in patients with BCG-unresponsive carcinoma in situ (CIS) with or without papillary tumours: and no disease progression to muscle-invasive or metastatic disease among patients with recurrent disease as of the time of analysis.[4] In addition, a preliminary analysis of phase I study combining intravesical BCG with pembrolizumab in high-grade NMIBC after treatment failure with at least two courses showed that the combination was safe with overall response rate of 69%.[5]
The current recommended treatment for high-risk NMIBC is trans urethral removal of bladder tumour (TURBT) and the choice of either intravesical BCG or radical cystectomy.[6] PD-L1 expression in the tumour microenvironment may attenuate responses to BCG[7]. A study showed that in high-risk NMIBC, the rate of recurrence in treatment with BCG alone was as high as 50% in the first three years of follow up.[8] Pembrolizumab in combination with BCG therapy will offer a novel approach in the treatment of this group of bladder cancer. Therefore, if licensed, pembrolizumab in combination with BCG may provide an important alternative to the existing therapies.

Regulatory & Development Status

Pembrolizumab in combination with various medicinal products is currently licensed in the UK for the following indications:[9-11]

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

- Colorectal cancer
- Triple negative breast cancer
- Endometrial carcinoma
- Cervical cancer
- Microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR) cancers like colorectal cancer, endometrial carcinoma, gastric cancer, small intestine cancer, and biliary cancer

Pembrolizumab is also currently in phase II and/or III development for a number of other indications including:[12]

- Prostate cancer
- Biliary tract cancer
- Ovarian cancer
- Bladder cancer
- Gastric cancer
- Multiple myeloma
- Pancreas cancer
- Medullary thyroid 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 NMIBC, whereas if the cells spread beyond the lining into the surrounding bladder muscle, this is muscle-invasive bladder cancer.[13] NMIBC is divided into three risk groups: low, intermediate (medium) and high. High risk NMIBC means the cancer is most likely to spread or return after treatment, so may require more treatment and closer monitoring.[14] 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.[13] Tobacco smoking is the most important risk factor for bladder cancer, causing 50% of the cases.[15] 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.[16]

In England in 2017, there were 8,686 newly diagnoses cases and 4,736 deaths registrations for malignant neoplasm of bladder (ICD-10 code C67) and a crude total death rate of 11.8 per 100,000 in men, and 5.2 per 100,000 in women[17] The age-standardised 1-year and 5–year survival for patients diagnosed with bladder cancer in England in 2017 was 74.1% and 52.6% respectively.[18] The 2021-2022 Hospital Episodes Statistics for England recorded a total of 68,614 finished consultant episodes (FCE) for malignant neoplasm of bladder, resulting in 64,584 hospital admissions, 88,955 FCE bed days and 40,978 day cases.[19]

Recommended Treatment Options

The current treatment options recommended by NICE for adults with NMIBC are:[6,20]

- If the first TURBT shows high-risk NMIBC, offer another TURBT as soon as possible and no later than 6 weeks after the first resection
- Offer the choice of intravesical BCG (Bacille Calmette-Guérin) or radical cystectomy to people with high-risk NMIBC cancer and base the choice on a full discussion with the person, the clinical nurse specialist and a urologist who performs both intravesical BCG and radical cystectomy.

Clinical Trial Information

Trial	**KEYNOTE-676,** NCT03711032, EudraCT 2018-001967-22; A Phase 3, Randomized, Comparator-controlled Clinical Trial to Study the Efficacy and Safety of Pembrolizumab (MK-3475) in Combination with Bacillus Calmette-Guerin (BCG) in Participants with High-risk Non-muscle Invasive Bladder Cancer (HR NMIBC) That is Either Persistent or Recurrent Following BCG Induction or That is Naïve to BCG Treatment **Phase III:** Recruiting **Location(s):** 12 EU countries, UK, USA, Canada, and other countries **Primary completion date**: December 2025
Trial Design	Randomised, parallel assignment, open label
Population	N=1405 (estimated); adult 18 years and older; confirmed histological diagnosis of high-risk non-muscle invasive and has undergone trans urethra removal of bladder tumour (TURBT).
Intervention(s)	Post-induction Cohort A: • BCG (Induction and Maintenance) in combination with 200 mg pembrolizumab administered IV every 3 weeks (Q3W) for 35 doses BCG Naïve Cohort B: • BCG (Induction and reduced or full maintenance) in combination with 400 mg pembrolizumab administered IV every 6 weeks (Q6W) for 9 doses
Comparator(s)	BCG monotherapy (Induction and Maintenance) via intravesical instillation
Outcome(s)	Primary outcome measures: • Complete Response Rate (CRR) by Blinded Independent Central Review (BICR) (Cohort A) [Time frame Up to 3.5 years] • Event-Free Survival (EFS) (Cohort B) [Time frame: Up to 5 years} See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The NHS indicative price for 1 vial of pembrolizumab(100mg/4ml) costs £2,630.00.[21]

Relevant Guidance

NICE Guidance

- NICE clinical guidance. Bladder cancer: diagnosis and management (NG2). Feb 2015.
- NICE interventional procedures guidance. Transurethral laser ablation for recurrent non-muscle-invasive bladder cancer. (IPG656). July 2019.
- NICE interventional procedures guidance. Electrically stimulated intravesical chemotherapy for non-muscle-invasive bladder cancer (IPG638). January 2019.
- NICE interventional procedure guidance. Intravesical microwave hyperthermia and chemotherapy for non-muscle-invasive bladder cancer (IPG628). September 2018.
- NICE medical technologies guidance. Synergo for non-muscle-invasive bladder cancer (MTG61). November 2021

NHS England (Policy/Commissioning) Guidance

- NHS England. Guidelines for the Management of Bladder Cancer. December 2016.
- 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 Non–muscle-invasive Bladder Cancer. 2022.[22]
- Powles T, Bellmunt J, Comperat E, et al., Bladder cancer: ESMO clinical practice guideline for diagnosis, treatment and follow-up. 2021[23]

Additional Information

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