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Health Technology Briefing
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Pembrolizumab with stereotactic body radiotherapy for unresected stage I or II non-small cell lung cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28853	NICE ID: 10705	UKPS ID: 666177

Licensing and Market Availability Plans

Currently in phase III/II trials.

Summary

Pembrolizumab with stereotactic body radiotherapy (SBRT) is currently in development for patients with unresected stage I or II (stage IIB N0, M0) non-small cell lung cancer (NSCLC). NSCLC is the most common type of lung cancer. Stage I NSCLC is small; contained inside the lung and has not spread to lymph nodes; and stage IIB is up to 5cm in size and has spread into nearby lymph nodes, or between 5cm and 7cm but has not spread into any lymph nodes. Unresected cancer is that which has not been either partly or completely removed by surgery. Some symptoms of lung cancer include persistent or chronic cough; coughing up blood; persistent breathlessness; loss of appetite or unexplained weight loss. Treatment options for unresected stage I or II NSCLC are however very limited.

Pembrolizumab is a monoclonal antibody, a protein that has been designed to recognise and block a receptor ('target') called PD-1. Some cancers can make a protein (PD-L1) that combines with PD-1 to switch off the activity of certain cells of the immune system, preventing them from attacking the cancer. By blocking PD-1, pembrolizumab stops the cancer switching off these immune cells, thereby increasing the immune system's ability to kill the cancer cells. Pembrolizumab is administered via intravenous (IV) infusion. Pembrolizumab preceded by SBRT has been shown to be a well-tolerated and promising treatment strategy to augment anti-tumour immune response. If licensed, a combination of pembrolizumab and SBRT will offer an additional treatment option for patients with unresected stage I or II (stage IIB N0, M0) NSCLC who currently have few effective therapies available.

Proposed Indication

Adult (18 years and older) patients with unresected stage I or II (stage IIB N0, M0) non-small cell lung cancer (NSCLC).[1]

Technology

Description

Pembrolizumab (Keytruda, MK-3475) 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]

Pembrolizumab with stereotactic body radiotherapy (SBRT) is currently in clinical development for patients with unresected stage I or II NSCLC. In the Phase III clinical trial (MK-3475-867/KEYNOTE-867; NCT03924869), participants received 200 mg of pembrolizumab via intravenous (IV) infusion once every 3 weeks for up to 17 cycles in addition to SBRT once every 3, 4, 5, or 8 fractions.[1]

Key Innovation

Radiotherapy potentially greatly reduces the growth of tumours, thus enabling patients to respond to immunotherapy (such as pembrolizumab) for longer periods of time. Radiation can be used to prime the tumour for immunotherapy by increasing the susceptibility of tumour cells to immune-mediated treatment. Moreover, combining immune modulating agents and radiation may induce protective immunologic memory, which could prevent disease recurrence.[3] The phase II trial (NCT02492568) showed that pembrolizumab preceded by SBRT resulted in a doubling of the overall response rate without increase in toxicity. This is a well-tolerated and promising treatment strategy to augment the anti-tumour immune response with checkpoint blockade.[4]

If licensed, pembrolizumab with SBRT will offer an additional treatment option for patients with unresected stage I or II (stage IIB N0, M0) NSCLC who currently have few effective therapies available.

Regulatory & Development Status

Pembrolizumab is already licensed in the EU/UK for the following indications:[2]

- Melanoma
- NSCLC (as monotherapy or in a combination for various subgroups)
- Classical Hodgkin lymphoma
- Urothelial carcinoma
- Head and neck squamous cell carcinoma
- Renal cell carcinoma
- Colorectal cancer
- Oesophageal carcinoma
- Triple-negative breast cancer
- Endometrial carcinoma

Pembrolizumab is in in phase III/II clinical development for various cancer indications, some of which include:[5]

- Hepatocellular carcinoma
- Melanoma
- Urothelial carcinoma
- Renal cell carcinoma
- Head-and-neck carcinoma
- Merkel cell carcinoma

Patient Group

Disease Area and Clinical Need

Lung cancer is the uncontrolled growth of abnormal cells in one or both lungs.[6] There are two major types of lung cancer, NSCLC and small cell lung cancer. NSCLC is the most common type of lung cancer, accounting for about 85% of lung cancers.[7] There are six stages of NSCLC. Stage I NSCLC means that the cancer is in the lung tissues but has not metastasized to lymph nodes. It is normally smaller than 4 cm. In some cases of stage IIB NSCLC, the lung cancer tumour measures 5 cm or smaller and has reached lymph nodes located in the same area of the chest as the original tumour—typically lymph nodes in the lung or close to the bronchus. In other cases of stage IIB, the cancer has not reached the lymph nodes but meets one of the following criteria: the tumour is smaller than 7 cm, but larger than 5 cm; or at least one additional tumour has formed in the same part of the lung where the original tumour was detected.[8] A person's risk of developing lung cancer depends on many factors including age, genetics and exposure to risk factors (including smoking, air pollution and ionising radiation).[9] There are usually no signs or symptoms in the early stages. Symptoms of lung cancer develop as the condition progresses. The main symptoms of lung cancer include persistent cough; chronic cough; recurring chest infections; coughing up blood; an ache or pain when breathing or coughing; persistent breathlessness; persistent tiredness or lack of energy; loss of appetite or unexplained weight loss.[10]

Lung cancer is the third most common cancer in the UK accounting for 13% of all new cancer cases (2016-2018).[11] In 2020-21, there were 86,043 hospital admissions with a primary diagnosis of malignant neoplasm of bronchus and lung (ICD-10 code C34) resulting in 103,856 finished consultant episodes (FCEs) and 170,030 FCE bed days.[12] According to the National Cancer Registration and Analysis Service (NCRAS), there were 7,656 diagnosed cases of stage I lung cancer and 2,955 diagnosed cases of stage II lung cancer in 2017 in England; this represents 27% of the overall number of lung cancer cases diagnosed for that year.[13] In England (2013-2017), the 1-year survival rate for people with stage I lung cancer was 87.7% and the 5-year survival rate was 56.6%. For people with stage II cancer, the 1-year survival rate was 73% and the 5-year survival rate was 34.1%.[14] In 2017 there were 30,131 registrations of death from cancer in England for malignant neoplasms of the trachea, bronchus and lung in England (ICD-10 code C33-34).[15]

Recommended Treatment Options

NICE recommends the following treatment options for unresected stage I or II NSCLC:[16]

- Radical radiotherapy with stereotactic ablative radiotherapy (SABR) or sublobar resection.

Clinical Trial Information

Trial	**MK-3475-867/KEYNOTE-867**, NCT03924869; EudraCT 2018-004320-11; A Phase 3, Randomized, Placebo-Controlled Clinical Study to Evaluate the Safety and Efficacy of Stereotactic Body Radiotherapy (SBRT) With or Without

	Pembrolizumab (MK-3475) in Participants With Unresected Stages I or II Non Small Cell Lung Cancer (NSCLC) **Phase III –** Recruiting **Location(s):** 7 EU countries, UK, USA, Canada and other countries
Trial Design	Randomised, parallel assignment, double-blinded, placebo-controlled
Population	N=530 (estimated); adults (18 years and older) who have previously untreated NSCLC confirmed as stage I or II (T1 to limited T3, N0, M0) and cannot undergo thoracic surgery
Intervention(s)	• SBRT once every 3, 4, 5, or 8 fractions over approximately 2 weeks • Pembrolizumab 200 mg (IV) once every 3 weeks for up to 17 cycles (up to approximately 1 year)
Comparator(s)	SBRT once every 3 days for 3, 4, 5, or 8 fractions + matched placebo
Outcome(s)	Primary outcome measures: • Event-free Survival (EFS) [time frame: up to approximately 58 months] • Overall Survival (OS) [time frame: up to approximately 68 months] See trial record for full list of other outcomes
Results (efficacy)	-
Results (safety)	-

Estimated Cost

Pembrolizumab is already marketed in the UK; a vial (25mg/ml) costs £2,630.[17]

Relevant Guidance

NICE Guidance

- NICE clinical guideline. Lung cancer: diagnosis and management (NG122). March 2019.
- NICE quality standard. Lung cancer in adults (QS17). March 2012.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for Cancer: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- National Comprehensive Cancer Network (NCCN). Non–Small Cell Lung Cancer, Version 5.2017, NCCN Clinical Practice Guidelines in Oncology. 2017.[18]
- Scottish Intercollegiate Guidelines Network. Management of lung cancer (SIGN 137). 2014.[19]

Additional Information

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