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Newcastle University

Health Technology Briefing
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Pembrolizumab with olaparib and chemoradiation for previously untreated limited-stage small-cell lung cancer

Company/Developer	Merck Sharp & Dohme Ltd

☐ New Active Substance ☒ Significant Licence Extension (SLE)

NIHRIO ID: 28523	NICE ID: Not available	UKPS ID: 666209

Licensing and Market Availability Plans

Currently in phase III clinical trials

Summary

Small cell lung cancer (SCLC) is an aggressive (fast-growing) cancer that forms in tissues of the lung and can spread to other parts of the body. Limited stage SCLC (LS-SCLC) means the cancer cells can be seen in one lung and in nearby lymph nodes. SCLC can affect anyone, but it typically affects people who have a long history of tobacco use. Some symptoms include chest discomfort, coughing up blood, shortness of breath. LS-SCLC remains a challenging disease with current standard of care treatment despite improvements in diagnosis and therapy during the past years.

Pembrolizumab, is a monoclonal antibody, a protein that has been designed to recognise and block a target called PD-1. By blocking PD-1, pembrolizumab increases the immune system's ability to kill the cancer cells. Olaparib blocks the action of an enzyme called human poly ADP ribose polymerase (PARP), which helps to repair damaged DNA in normal and cancer cells during cell division. When PARP is blocked, the damaged DNA in cancer cells cannot be repaired and, as a result, the cancer cells die. Pembrolizumab is administered intravenously and olaparib, orally. If licensed, pembrolizumab in combination with olaparib following concurrent chemoradiation therapy with pembrolizumab will offer an additional treatment option for newly diagnosed, treatment-naïve adult patients with LS-SCLC.

Proposed Indication

For the first-line treatment of newly diagnosed adult patients with limited-stage (stage I-III) small cell lung cancer (LS-SCLC).[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 programmed death ligand 1 (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] Olaparib is a potent inhibitor of human poly (ADP-ribose) polymerase enzymes (PARP-1, PARP-2, and PARP-3), and has been shown to inhibit the growth of selected tumour cell lines in vitro and tumour growth in vivo. PARPs are required for the efficient repair of DNA single strand breaks. When olaparib is bound to the active site of DNA-associated PARP it prevents the dissociation of PARP and traps it on the DNA, thus blocking repair.[3] As a result, the damaged DNA in cancer cells cannot be repaired and this causes the cancer cells to die.[4]

Pembrolizumab in combination with olaparib is in clinical development to be administered following concurrent chemoradiation therapy with pembrolizumab in newly diagnosed, treatment-naïve adult patients with LS-SCLC. In the phase III clinical trial, KEYLYNK-013 (NCT04624204), participants will receive 4 cycles of standard-of-care chemotherapy (etoposide/platinum) plus pembrolizumab 200 mg every 3 weeks concurrently with standard thoracic radiotherapy, followed by 9 cycles of pembrolizumab 400 mg every 6 weeks plus olaparib 300 mg twice daily for 12 months or until specific discontinuation criteria are met.[1]

Key Innovation

The current standard of care for patients with newly diagnosed LS-SCLC is concurrent chemoradiotherapy. The prognosis remains poor due to the aggressiveness and high risk of progression or relapse of SCLC even if an initial response is achieved. Therefore, there is an urgent unmet clinical need in this population.[5] Concurrent chemoradiotherapy with etoposide and platinum (carboplatin/cisplatin) pembrolizumab has shown antitumor activity and acceptable safety in patients with LS-SCLC. Olaparib, has also shown clinical activity in combination with checkpoint inhibitors (pembrolizumab) in patients with SCLC.[6] In a recent preclinical study where olaparib was combined with an anti- PD-L1 agent, there was increased PD-L1 expression and cytotoxic T-cell infiltration, decreased T-cell exhaustion, and significant tumour regression in the SCLC group.[7]

If licensed, pembrolizumab in combination with olaparib following concurrent chemoradiation therapy with pembrolizumab will offer an additional treatment option for newly diagnosed, treatment-naïve adult patients with LS-SCLC.

Regulatory & Development Status

Pembrolizumab in combination with olaparib does not currently have Marketing Authorisation in the EU/UK for any indication.

In the EU/UK, pembrolizumab in combination has Marketing Authorisation for the following:[2]

- Non-small cell lung cancer
- Renal cell carcinoma
- Endometrial carcinoma
- Oesophageal carcinoma
- Breast cancer
- Cervical cancer
- Gastric or gastro-oesophageal junction adenocarcinoma

In the EU/UK, olaparib in combination has Marketing Authorisation for the following:[3]

- Ovarian cancer
- Breast cancer
- Prostate cancer

Pembrolizumab in combination with olaparib is in phase II/III clinical development for the following:[8]

- Solid tumours
- Breast cancer
- Uveal melanoma
- Ocular melanoma
- Endometrial carcinosarcoma
- Extensive stage SCLC
- Ovarian cancer
- Glioma
- Non-small cell lung cancer
- Gastric cancer
- Head and neck cancer
- Pancreatic cancer
- Prostate cancer
- Cervical cancer

Patient Group

Disease Area and Clinical Need

SCLC is a malignant epithelial tumour arising from cells lining the lower respiratory tract. The tumour cells are small and densely packed, with scant cytoplasm, finely granular nuclear chromatin, and absence of nucleoli.[9] It is a rare fast-growing lung cancer that can affect anyone, but it typically affects people who have a long history of tobacco use, specifically smoking cigarettes.[10] Limited stage means that the cancer is limited to the thorax and radiation therapy could be a treatment option. About 1 out of 3 people with SCLC have limited stage disease when first diagnosed.[11] This generally means that the cancer is in one lung or may be in nearby lymph nodes, for example, in the centre of the chest or above the collar bone.[12] Smoking tobacco is the cause of most lung cancers and the biggest risk factor. This includes smoking cigarettes, cigars, and pipes.[13] Other risk factors of SCLC include: smoking (including second-hand smoke); exposure to radiation from cancer treatments or imaging scans; exposure to radon gas; exposure to workplace hazards like asbestos, arsenic, nickel, tar or toxic chemicals; family history of lung cancer; and having human immunodeficiency virus.[10] Symptoms of SCLC include coughing and shortness of breath. Other symptoms include chest discomfort or pain, wheezing, blood in sputum, hoarseness, trouble swallowing, loss of appetite, weight loss for no known reason, tiredness, and swelling in the face and/or veins in the neck.[14]

Lung cancer is the 3rd most common cancer in the UK, accounting for 13% of all new cancer cases (2016-2018).[15] SCLC makes up about 15% of lung cancers.[16] Only about 33% people with SCLC have limited stage cancer when it is first found.[17] In England, for patients diagnosed with stage I lung cancer between 2013 and 2017, the age-standardised 1-year and 5-year survival rate was 87.7% and 56.6% respectively. For patients diagnosed with stage II lung cancer, the age-standardised 1-year and 5-year survival rate was 73% and 34.1% respectively. For patients diagnosed with stage III lung cancer, the age-standardised 1-year and 5-year survival rate was 48.7% and 12.6% respectively.[18] In England (2022-23), there were 122,866 finished consultant episodes (FCE) and 104,232 admissions for malignant neoplasm of bronchus and lung, unspecified (ICD-10 code C34.0), resulting in 80,131 day cases and 217,569 FCE bed days.[19] In England (2017), there were 38,888 newly diagnosed cases of malignant neoplasm of bronchus and lung (ICD-10 code C34) and 28,170 registered deaths.[20]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) currently recommends cisplatin-based combination chemotherapy, and radiotherapy with concurrent chemotherapy for the first-line treatment of limited-stage small-cell lung cancer.[21]

Clinical Trial Information

Trial	**KEYLYNK-013; NCT04624204, EudraCT 2019-003616-31;** A Randomized, Double-blind, Placebo-controlled Phase 3 Study of Pembrolizumab (MK-3475) in Combination With Concurrent Chemoradiation Therapy Followed by Pembrolizumab With or Without Olaparib (MK-7339), Compared to Concurrent Chemoradiation Therapy Alone in Participants With Newly Diagnosed Treatment-Naïve Limited-Stage Small Cell Lung Cancer (LS-SCLC) **Phase III** - Recruiting **Locations:** 11 EU countries, UK, USA, Canada, and other countries **Primary completion date:** October 2027
Trial Design	Randomised, parallel assignment, triple-blind, placebo-controlled
Population	N= 672 (planned); subjects with LS-SCLC who have not received prior treatment
Intervention(s)	• Pembrolizumab • Olaparib • Etoposide • Carboplatin • Radiation
Comparator(s)	Matched placebo
Outcome(s)	Primary outcomes: • Progression-free Survival Per Response Evaluation Criteria in Solid Tumours Version 1.1 (RECIST 1.1); the time from randomization to progression or death due to any cause, whichever occurs first (Time Frame: Up to approximately 59 months) • Overall Survival: the time from randomization to death due to any cause (Time Frame: Up to approximately 82 months) See trial record for full list of other outcomes

Results (efficacy)	-
Results (safety)	-

Estimated Cost

A 100mg vial of pembrolizumab infusion (25mg per 1ml) costs £2,630.[22]
A pack of 56 tablets of Olaparib 100mg costs £2,317.[23]

Relevant Guidance

NICE Guidance

- NICE technology appraisal in development. Durvalumab with tremelimumab for treating limited-stage small-cell lung cancer after chemoradiation. Expected date of issue to be confirmed.
- NICE technology appraisal in development. Durvalumab for treating limited-stage small-cell lung cancer after chemoradiation. Expected date of issue to be confirmed.
- NICE guideline. Suspected cancer: recognition and referral (NG12). October 2023.
- NICE guideline. Lung cancer: diagnosis and management (NG122). July 2023.
- NICE quality standard. Lung cancer in adults (QS17). December 2019.
- NICE quality standard. Suspected cancer (QS124). December 2017.

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: Radiotherapy (All Ages). B01/S/a.

Other Guidance

- National Comprehensive Cancer Network (NCCN). Small Cell Lung Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. December 2021.[24]
- European Society for Medical Oncology (ESMO). Small-cell lung cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment, and follow-up. July 2021.[25]
- NHS Northern Cancer Alliance. Lung Cancer Clinical Guidelines. May 2019.[26]
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Additional Information

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